1. Obesity, Heart Disease, and Favorable Prognosis—Truth or Paradox?  
*Pages 825-826*  
Carl J. Lavie, Richard V. Milani and Hector O. Ventura

2. Diagnosis of Acute Pulmonary Embolism: Always Be Vigilant  
*Pages 827-828*  
Samuel Z. Goldhaber

**Review**

3. Impact of Diabetes on the Severity of Liver Disease  
*Pages 829-834*  
Ingrid J. Hickman and Graeme A. Macdonald

**Office management: geriatrics**

4. Considerations for the Diagnosis and Treatment of Testosterone Deficiency in Elderly Men  
*Pages 835-840*  
Mohammed Kazi, Stephen A. Geraci and Christian A. Koch

5. Orthostatic Hypotension in the Elderly: Diagnosis and Treatment  
*Pages 841-847*  
Vishal Gupta and Lewis A. Lipsitz

**Diagnostic dilemma**

6. Fact or Factitious?  
*Pages 848-850*  
Stefan Jenni, Beat Gloor, Christoph Stettler and Emanuel R. Christ

7. Over the Speed Limit  
*Pages 851-853*  
Melissa R. Robinson, Ryan A. Brown, Uma Srivatsa and Ezra A. Amsterdam

**Images in dermatology**

8. Board Stiff  
*Pages 854-856*  
Peter Mattei, Julie Templet and Carrie Cusack
9. **A Heart Aflutter**  
   *Pages 857-859*  
   Ahmad Khraisat, Sarabjeet Singh, Rohit Arora and Eshraq Al-Jaghbeer

10. **No Simple Sore Throat**  
    *Pages 860-862*  
    William J. Salyers Jr., Christina Schnose and Adam Zarchan

11. **Obesity Paradox in Patients with Hypertension and Coronary Artery Disease**  
    *Pages 863-870*  
    Seth Uretsky, Franz H. Messerli, Sripal Bangalore, Annette Champion, Rhonda M. Cooper-DeHoff, Qian Zhou and Carl J. Pepine

12. **Clinical Characteristics of Patients with Acute Pulmonary Embolism: Data from PIOPED II**  
    *Pages 871-879*  

13. **Thyroid Function Abnormalities during Amiodarone Therapy for Persistent Atrial Fibrillation**  
    *Pages 880-885*  
    Elizabeth L. Batcher, X. Charlene Tang, Bramah N. Singh, Steven N. Singh, Domenic J. Reda and Jerome M. Hershman

14. **Randomized Trial to Improve Fracture Prevention in Nursing Home Residents**  
    *Pages 886-892*  
    Cathleen S. Colón-Emeric, Kenneth W. Lyles, Paul House, Deborah A. Levine, Anna P. Schenck, Jeroan Allison, Joel Gorospe, Mary Fermazin, Kristi Oliver, Jeffrey R. Curtis, Norman Weissman, Aiyuan Xie and Kenneth G. Saag

15. **Impact of a Fluoroquinolone Restriction Policy in an Elderly Population**  
    *Pages 893-900*  
    Muhammad Mamdani, David McNeely, Gerald Evans, Janet Hux, Paul Oh, Natalie Forde and John Conly

    *Pages 901.e1-901.e13*  
    Angelia Kirkpatrick, Suman Rathbun, Thomas Whitsett and Gary Raskob
### AJM online

#### Review

17. **Diagnostic Evaluation of Mononucleosis-Like Illnesses**  
   *Pages 911.e1-911.e8*  
   Christopher Hurt and Dominick Tammaro

#### Clinical research study

18. **Incidence and Clinical Spectrum of Thiazide-associated Hypercalcemia**  
   *Pages 911.e9-911.e15*  
   Robert A. Wermers, Ann E. Kearns, Gregory D. Jenkins and L. Joseph Melton III

#### Erratum

19. **Erratum**  
   *Page 911*

#### Clinical communications to the editor

20. **Marinol-Induced Gynecomastia: A Case Report**  
    *Page e1*  
    Rebekah C. Allen, Anne Marie Wallace and Melanie Royce

21. **Sarcoidosis Manifesting as a Periorbital Purplish Rash**  
    *Pages e3-e4*  
    Mitsuhito Ota, Daigo Nakazawa and Daisuke Sawamura

#### Letters

22. **Alcohol and Gout**  
    *Page e5*  
    Hyon K. Choi and Gary Curhan

23. **The Reply**  
    *Page e7*  
    Yuqing Zhang, Tuhina Neogi and David J. Hunter

24. **Functional Status in Chronic Obstructive Pulmonary Disease**  
    *Page e9*  
    Andrea Corsonello, Claudio Pedone and Raffaele Antonelli Incalzi

25. **The Reply**  
    *Page e11*  
    Richard ZuWallack
26. Broadening the Differential Diagnosis from a Different Perspective  
   Page e13  
   Oscar M. Jolobe

27. Effective Detection of Celiac Disease Using Salivary Anti-transglutaminase  
   Page e15  
   Annick Ocmant and Françoise Mascart

28. The Reply  
   Page e17  
   Peter H.R. Green

29. Noninvasive Ventilation in Acute Heart Failure  
   Page e19  
   Ritesh Agarwal and Rajagopala Srinivas

30. The Reply  
   Page e21  
   John R. Kapoor and Mark A. Perazella

31. Endothelium-Independent Microvascular Dysfunction in Cardiac Syndrome X  
   Page e23  
   Pankaj Madan and Ritu Madan

32. The Reply  
   Page e25  
   Christopher P. Appleton and R. Todd Hurst

APM perspectives

33. Communication Skills: A Call for Teaching to the Test  
   Pages 912-915  
   Anna Headly

Medical humanities perspectives

34. The Heroic Physician and The Gross Clinic  
   Pages 916-917  
   Helle Mathiasen
Obesity, Heart Disease, and Favorable Prognosis—Truth or Paradox?

The words of truth are always paradoxical.
—Lao Tzu

Despite the fact that obesity has been shown to be an independent risk factor for cardiovascular disease (CVD),1,2 many studies have demonstrated that obese patients with established CVD have a better prognosis than do patients with “ideal” body weight—the so called obesity-paradox. This paradox has been best described for patients with advanced systolic heart failure (HF),3,4 including those where a higher percentage of body fat was the strongest predictor of event-free survival.4 In advanced HF, obese patients can present earlier because of reduced circulating natriuretic peptides, as well as being more severely symptomatic due to non-HF factors, including deconditioning and restrictive lung disease. Additionally, cachexia and non-purposeful weight loss are associated with a particularly poor prognosis.3,4 Likewise, the paradoxical relationship between obesity and prognosis also is noted in patients with advanced cancers, end-stage renal disease, and in the very elderly.3

In the present issue of The American Journal of Medicine, Uretsky et al5 demonstrate that in a large population with hypertension and coronary heart disease (CHD), overweight and obese patients had decreased risk of major CVD events, particularly mortality, compared with “normal” weight patients. These data are in agreement with a recent meta-analysis by Romero-Corral et al that demonstrated better CVD outcomes in overweight and mildly obese CHD patients compared with those with ideal weight and especially compared with underweight patients (who generally have the worst prognosis in most studies).6 In addition, it also supports the results of a recent study from nearly 7000 male non-HF veterans referred for stress testing that demonstrated a similar obesity paradox.7 Nevertheless, the manuscript by Uretsky et al5 is still noteworthy, in that they studied nearly 23,000 hypertensives with CHD who were vigorously treated. One of the limitations, as in most studies, is that non-purposeful weight loss, which would be associated with a poor prognosis, was not assessed. Although the underlying reasons for the obesity paradox in this cohort are not well understood, it is possible that obese hypertensives have lower systemic vascular resistance as well as plasma renin activity compared with lean hypertensives, and these hemodynamic parameters and neurohormonal mechanisms might contribute to their better prognosis.

Although improved outcomes appear to be a consistent association with increased body weight, one should not conclude that weight reduction is detrimental in overweight populations. We previously demonstrated that obese subjects with CHD who were more successful with weight reduction had considerably greater improvements in most CHD risk factors following rehabilitation compared with obese subjects who did not lose weight.2 Likewise, in a study of over 1500 CHD patients, intentional weight loss from a 6-month diet produced lower incidence of CHD events over 4 years.8 These studies support purposeful weight reduction in obese CHD patients, despite the “obesity paradox.”

Finally, we must not lose sight of the fact that obesity might be intimately involved in the pathogenesis of hypertension and CHD; therefore, without significant weight gain, many of the overweight and obese patients in the INternational VErapamil SR-trandolopril STudy (INVEST) might not have developed hypertension and/or CHD in the first place. As we continue to investigate the obesity paradox in CVD, including CHD, we should remember the old proverb, “Only one thing is certain—that is nothing is certain.”

Carl J. Lavie, MD
Richard V. Milani, MD
Hector O. Ventura, MD
Department of Cardiovascular Diseases
Ochsner Medical Center
New Orleans, La
clavie@ochsner.org

References
2. Lavie CJ, Milani RV. Effects of cardiac rehabilitation, exercise training, and weight reduction on exercise capacity, coronary risk factors, be-


Chest CT scanning has heralded unprecedented advances in the diagnosis of pulmonary embolism. Multiplanar imaging permits detection of sub-millimeter thrombi so small that their clinical importance may be uncertain. Can we now rely upon these technological achievements to substitute for the art of clinical diagnosis?

Failure to identify pulmonary embolism because the diagnosis is not considered remains the last major problem confronting successful detection of pulmonary embolism. If the health care provider, patient, and family are not aware of the risk factors and common clinical presentations of pulmonary embolism, the diagnosis will be overlooked. Many laypersons do not even know what a pulmonary embolism is.

Unfortunately, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II informs us that the clinical presentation of acute pulmonary embolism remains as elusive as ever. The number one symptom was rapid onset dyspnea at rest, usually within seconds to hours. The second most common symptom was pleuritic chest pain. Third was cough, in 43%, though I find cough a rare symptom in the pulmonary embolism patients whom I evaluate. The most common signs were nonspecific: tachypnea and tachycardia.

Symptoms of pulmonary embolism are often accompanied by symptoms of deep vein thrombosis such as calf or thigh pain. This can be a helpful hint. In PIOPED II, the presence of calf or thigh pain was the symptom that most commonly differed between patients with and without pulmonary embolism. Similarly, the presence of calf or thigh edema, erythema, tenderness, or a palpable cord was the principal sign differentiating pulmonary embolism from no pulmonary embolism in PIOPED II.

Of special concern in PIOPED II is that 18% of those with pulmonary embolism had a low probability clinical assessment. Even in patients ultimately discovered to have main or lobar pulmonary embolism, 15% had low clinical probability.

Thus, the diagnosis of pulmonary embolism remains an art as well as a science. We must acknowledge that this area of medicine lacks an entirely satisfactory nomogram or clinical decision algorithm. The weakness in diagnostic approach is at the most crucial decision-making point—whether suspicion of pulmonary embolism is justified based upon clinical presentation.

PIOPED II captures the clinical characteristics of a special type of patient with suspected pulmonary embolism who agrees to undergo an extensive series of diagnostic tests far beyond the usual combination of D-dimer blood testing and chest CT scan. Patients were excluded if they had critical illness, abnormal serum creatinine, contrast allergy, pregnancy, treatment with long-term anticoagulants, or an inferior vena caval filter. We should keep in mind that PIOPED II might not represent the “typical pulmonary embolism patient” in the “real world.”

When I evaluate patients for pulmonary embolism, I find the clinical setting and classical risk factors especially useful, along with the presence of a family history of pulmonary embolism. I believe that unexplained dyspnea, usually at rest but sometimes with exertion, is the most useful symptom of pulmonary embolism. Anxiety, difficulty to define but easy to recognize, has provided for me a useful general sign. I have learned that the absence of tachypnea or tachycardia is quite frequent in young pulmonary embolism patients and in those without prior cardiopulmonary disease. A useful clue in patients who appear ill is the soft systolic murmur of tricuspid regurgitation, heard at the left lower sternal border, with respiratory variation in the murmur’s location within systole and in the murmur’s intensity.

In summary, be vigilant for the possibility of acute pulmonary embolism because it can be elusive. This is especially important when patients with confirmed pneumonia or congestive heart failure do not improve with standard therapy. They may be suffering from concomitant pulmonary embolism. Remember that the clinical
setting is of paramount importance. Undertake a thorough history, including family history, and make careful observations during the physical examination regarding general appearance and vital signs, including a personally counted respiratory rate. Pay special attention to the cardiac and leg examinations. More widespread education of practitioners and the public about the potentially vague presentation of pulmonary embolism will raise awareness, improve vigilance, and result in fewer missed cases of this potentially fatal illness.

Reference
The prevalence of type 2 diabetes is increasing with a new diagnosis made every 21 seconds. Historically, the development of diabetes in patients with cirrhosis is well documented with overt diabetes present in up to 70% of cirrhotic subjects. However, evidence is emerging that the development of chronic liver disease and progression to cirrhosis may occur after the diagnosis of diabetes and that diabetes plays a role in the initiation and progression of liver injury. This article provides an overview of the evidence for an increased prevalence of diabetes in a range of liver diseases; the effect of diabetes on the severity of disease; the potential mechanisms whereby coexistent diabetes exacerbates progression of hepatic fibrosis; and the impact of obesity, insulin resistance, and type 2 diabetes on clinical outcomes. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Cirrhosis; Fatty liver disease; Insulin resistance; Obesity

The prevalence of type 2 diabetes is higher in patients who have liver diseases, such as nonalcoholic fatty liver disease, chronic viral hepatitis, hemochromatosis, alcoholic liver disease, and cirrhosis. The development of diabetes in patients with cirrhosis is well recognized, but evidence is emerging that the development of chronic liver disease and progression to cirrhosis may occur after the diagnosis of diabetes and that diabetes plays a role in the initiation and progression of liver injury. This article provides an overview of the evidence for an increased prevalence of diabetes in a range of liver diseases; the effect of diabetes on the severity of disease; the potential mechanisms whereby coexistent diabetes exacerbates progression of hepatic fibrosis; and the impact of obesity, insulin resistance, and type 2 diabetes on clinical outcomes. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Cirrhosis; Fatty liver disease; Insulin resistance; Obesity

The prevalence of type 2 diabetes is higher in patients who have liver diseases, such as nonalcoholic fatty liver disease, chronic viral hepatitis, hemochromatosis, alcoholic liver disease, and cirrhosis. The development of diabetes in patients with cirrhosis is well recognized, but evidence is emerging that the development of chronic liver disease and progression to cirrhosis may occur after the diagnosis of diabetes and that diabetes plays a role in the initiation and progression of liver injury. This article provides an overview of the evidence for an increased prevalence of diabetes in a range of liver diseases; the effect of diabetes on the severity of disease; the potential mechanisms whereby coexistent diabetes exacerbates progression of hepatic fibrosis; and the impact of obesity, insulin resistance, and type 2 diabetes on clinical outcomes. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Cirrhosis; Fatty liver disease; Insulin resistance; Obesity

The prevalence of type 2 diabetes is increasing with a new diagnosis made every 21 seconds. Historically, the development of diabetes in patients with cirrhosis is well documented with overt diabetes present in up to 70% of cirrhotic subjects. However, evidence is emerging that the development of chronic liver disease and progression to cirrhosis may occur after the diagnosis of diabetes and that diabetes plays a role in the initiation and progression of liver injury. This article provides an overview of the evidence for an increased prevalence of diabetes in a range of liver diseases; the effect of diabetes on the severity of disease; the potential mechanisms whereby coexistent diabetes exacerbates progression of hepatic fibrosis; and the impact of obesity, insulin resistance, and type 2 diabetes on clinical outcomes. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Cirrhosis; Fatty liver disease; Insulin resistance; Obesity

The prevalence of type 2 diabetes is increasing with a new diagnosis made every 21 seconds. Historically, the development of diabetes in patients with cirrhosis is well documented with overt diabetes present in up to 70% of cirrhotic subjects. However, evidence is emerging that the development of chronic liver disease and progression to cirrhosis may occur after the diagnosis of diabetes and that diabetes plays a role in the initiation and progression of liver injury. This article provides an overview of the evidence for an increased prevalence of diabetes in a range of liver diseases; the effect of diabetes on the severity of disease; the potential mechanisms whereby coexistent diabetes exacerbates progression of hepatic fibrosis; and the impact of obesity, insulin resistance, and type 2 diabetes on clinical outcomes. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Cirrhosis; Fatty liver disease; Insulin resistance; Obesity

The prevalence of type 2 diabetes is increasing with a new diagnosis made every 21 seconds. Historically, the development of diabetes in patients with cirrhosis is well documented with overt diabetes present in up to 70% of cirrhotic subjects. However, evidence is emerging that the development of chronic liver disease and progression to cirrhosis may occur after the diagnosis of diabetes and that diabetes plays a role in the initiation and progression of liver injury. This article provides an overview of the evidence for an increased prevalence of diabetes in a range of liver diseases; the effect of diabetes on the severity of disease; the potential mechanisms whereby coexistent diabetes exacerbates progression of hepatic fibrosis; and the impact of obesity, insulin resistance, and type 2 diabetes on clinical outcomes. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Cirrhosis; Fatty liver disease; Insulin resistance; Obesity

The prevalence of type 2 diabetes is increasing with a new diagnosis made every 21 seconds. Historically, the development of diabetes in patients with cirrhosis is well documented with overt diabetes present in up to 70% of cirrhotic subjects. However, evidence is emerging that the development of chronic liver disease and progression to cirrhosis may occur after the diagnosis of diabetes and that diabetes plays a role in the initiation and progression of liver injury. This article provides an overview of the evidence for an increased prevalence of diabetes in a range of liver diseases; the effect of diabetes on the severity of disease; the potential mechanisms whereby coexistent diabetes exacerbates progression of hepatic fibrosis; and the impact of obesity, insulin resistance, and type 2 diabetes on clinical outcomes. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Cirrhosis; Fatty liver disease; Insulin resistance; Obesity

The prevalence of type 2 diabetes is increasing with a new diagnosis made every 21 seconds. Historically, the development of diabetes in patients with cirrhosis is well documented with overt diabetes present in up to 70% of cirrhotic subjects. However, evidence is emerging that the development of chronic liver disease and progression to cirrhosis may occur after the diagnosis of diabetes and that diabetes plays a role in the initiation and progression of liver injury. This article provides an overview of the evidence for an increased prevalence of diabetes in a range of liver diseases; the effect of diabetes on the severity of disease; the potential mechanisms whereby coexistent diabetes exacerbates progression of hepatic fibrosis; and the impact of obesity, insulin resistance, and type 2 diabetes on clinical outcomes. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Cirrhosis; Fatty liver disease; Insulin resistance; Obesity
Nonalcoholic Fatty Liver Disease

The most prevalent liver disease in developed countries is nonalcoholic fatty liver disease, which occurs when there is lipid accumulation within the hepatocytes. This can be associated with hepatocyte injury and inflammation that results in hepatic fibrosis and ultimately in cirrhosis. This more severe end of the disease spectrum is described as nonalcoholic steatohepatitis. It is estimated that up to one third of adult Americans may have nonalcoholic fatty liver disease, whereas the prevalence of nonalcoholic steatohepatitis is estimated to be 2% to 3%. Nonalcoholic fatty liver disease is considered the most common cause of cryptogenic cirrhosis. It is associated with central obesity, and virtually all patients have evidence of insulin resistance. It is therefore not surprising that type 2 diabetes is present in 21% to 45% of patients with nonalcoholic fatty liver disease and is associated with a 2 to 5-fold increased risk for nonalcoholic fatty liver disease.

Viral Hepatitis

Evidence has accumulated regarding the association between glucose metabolism and chronic hepatitis C virus (HCV) infection. The National Health and Nutrition Examination Survey identified a 3-fold increased risk of type 2 diabetes in subjects who were aged more than 40 years and had chronic HCV, compared with HCV-negative participants. Knobler et al showed the prevalence of type 2 diabetes to be 33% in noncirrhotic patients with HCV compared with 5.6% in a control group. The reason for the link between HCV infection and type 2 diabetes may relate to viral effects because specific HCV genotypes (particularly genotype 1) have been linked to insulin resistance, and in vitro studies have demonstrated HCV proteins inhibiting insulin signaling.

In hepatitis B virus (HBV) infection, there is conflicting evidence as to whether there is an increased prevalence of type 2 diabetes. Knobler et al found that the prevalence of diabetes was twice as high in noncirrhotic subjects with HBV infection compared with controls without liver disease (12% vs 5.6%), although this difference was not statistically significant. Two other studies failed to show an association between type 2 diabetes and HBV.

Hemochromatosis

Hereditary hemochromatosis type 1 is the most prevalent cause of iron accumulation in populations with Northern European ancestry and is caused by mutations of HFE. Its association with diabetes is well recognized. Up to 23% of probands and 13% of family members with previously undiagnosed hemochromatosis have diabetes. The pathogenesis of diabetes in hemochromatosis relates in part to the deposition of iron in the pancreas. This iron accumulation occurs predominantly in exocrine cells; however, iron-containing granules can be shown to accumulate in islet cells, particularly in insulin-secreting beta-cells. Similar findings are present in the pancreas of iron-loaded animals. It might therefore be expected that hemochromatosis would be more prevalent in subjects with diabetes. Conte et al found an increased prevalence of hemochromatosis in individuals with type 2 diabetes. Others have detected an increased prevalence of HFE mutations in type 2 diabetes, but this has not been universal. Dubois-Laforgue et al found that although the prevalence of HFE mutations was not increased in type 2 diabetes, type 2 diabetic patients with HFE mutations had greater iron stores and were less likely to be obese.

Alcoholic Liver Disease

Patients with alcoholic liver disease have been shown to be at increased risk for type 2 diabetes. In a prospective follow-up study of 8663 men, heavy drinking (>270 g/wk) was associated with a 2-fold increased risk of developing type 2 diabetes compared with moderate drinking (60-120 g/wk). This association was independent of other risk factors, such as age, obesity, smoking history, family history of diabetes, and blood pressure. It is noteworthy that similar studies have not shown the same relationship in women. Excessive alcohol intake may have a direct effect on the development of type 2 diabetes by decreasing insulin-mediated glucose uptake in the acute situation and by damaging pancreatic islet cells with chronic use.

CIRRHOSIS AND DIABETES

The term “hepatogenous” diabetes is used to describe the association between cirrhosis and impaired glucose metabolism. Up to 96% of patients with cirrhosis have diabetes or impaired glucose tolerance. Hepatogenous diabetes differs from type 2 diabetes in that there is less association with risk factors such as age, body mass index, and family history of diabetes. Cirrhosis may contribute to the development of type 2 diabetes through numerous factors. With the development of portal hypertension, blood shunting redirects blood away from hepatocytes and results in re-
duced insulin clearance with peripheral hyperinsulinemia.\textsuperscript{31} This systemic hyperinsulinemia may contribute to the development of insulin resistance through the down-regulation of insulin receptors.\textsuperscript{32}

However, cirrhosis alone does not always induce diabetes, and the cause of liver disease and environmental factors may play a role. Zein et al\textsuperscript{26} found that the prevalence of diabetes was increased in HCV cirrhosis (25\%) and alcoholic liver disease (19\%) but not in cholestatic liver disease (1.3\%).

This association among diabetes, insulin resistance, and liver disease has implications with respect to treatment. The peroxisome proliferator-activated receptor-gamma agonists pioglitazone and rosiglitazone have shown promise in small studies of patients with nonalcoholic steatohepatitis, including cirrhotic patients\textsuperscript{33-35}; however, there are concerns about their use in patients with alanine aminotransferase 2.5 times or more the upper limit of normal or with decompensated cirrhosis.\textsuperscript{36} Long-term efficacy studies have not been completed. Similarly, metformin has shown some promise in the treatment of nonalcoholic steatohepatitis.\textsuperscript{37} although there are concerns about its use in advanced liver disease.

THE LINK BETWEEN OBESITY AND INSULIN RESISTANCE AND LIVER INJURY

Hepatic steatosis, obesity, and insulin resistance seem to act as cofactors for liver injury in a range of liver diseases.\textsuperscript{38} In patients with nonalcoholic fatty liver disease, older age, obesity, and the presence of type 2 diabetes are independent risk factors for more severe fibrosis.\textsuperscript{39} Obesity-related insulin resistance plays a clear role in the production of reactive oxygen species and altered adipokine production, which in turn leads to up-regulation of proinflammatory cytokines. Insulin resistance results in enhanced hepatic gluconeogenesis and impaired hepatic lipid metabolism, which results in hepatic steatosis and liver injury.\textsuperscript{40}

Obesity and steatosis are associated with more severe fibrosis in chronic HCV.\textsuperscript{41} Although steatosis in HCV is linked to genotype-specific viral effects, steatosis is more prevalent and worsened in obese, insulin-resistant patients irrespective of viral genotype.\textsuperscript{42} Emerging evidence supports the hypothesis that altered metabolic profiles associated with insulin resistance contribute to liver injury in HCV.\textsuperscript{43} Insulin resistance is an independent predictor for the rate of fibrosis progression,\textsuperscript{15} and elevated fasting insulin\textsuperscript{44,45} and glucose\textsuperscript{46} independently seem to contribute to fibrosis in HCV.

Hemochromatosis is another liver disease for which coexistent obesity and steatosis seem to contribute to liver injury.\textsuperscript{47} In a retrospective study of patients with hemochromatosis before de-ironing, obesity was independently associated with the presence of steatosis, which in turn was associated with more severe fibrosis.\textsuperscript{47} The prevalence of diabetes or degree of insulin resistance was not reported in this study.

In a study of 1604 alcoholic patients, Naveau et al\textsuperscript{48} found that being overweight was associated with a greater prevalence of alcoholic hepatitis and cirrhosis (60\% vs 35\% in lean patients).\textsuperscript{48} The mechanisms whereby obesity and insulin resistance may exacerbate liver injury in alcoholic liver disease are still debated. Alterations in cytokine production (leptin, adiponectin, and tumor necrosis factor-\textalpha) caused by both obesity and alcohol, may work synergistically to activate hepatic stellate cells, resulting in hepatic fibrosis.\textsuperscript{49}

TYPE 2 DIABETES MELLITUS AND THE SEVERITY OF LIVER DISEASE

There is evidence from a range of liver diseases linking obesity with insulin resistance and hepatic steatosis, which in turn contribute to liver injury. In nonalcoholic fatty liver disease, a range of studies have consistently identified type 2 diabetes as an independent predictor of fibrosis,\textsuperscript{39,50-52} faster fibrosis progression,\textsuperscript{51} and increased mortality.\textsuperscript{53} This relationship is maintained when analysis is restricted to noncirrhotic patients.\textsuperscript{51} Younossi et al\textsuperscript{54} demonstrated that patients with type 2 diabetes were at greater risk for the development of adverse outcomes such as cirrhosis or liver-related mortality.\textsuperscript{54}

Scrutiny of the impact of type 2 diabetes in HCV has identified a role for insulin resistance and type 2 diabetes in disease progression. Hyperinsulinemia,\textsuperscript{42} hyperglycemia,\textsuperscript{46} and insulin resistance\textsuperscript{55} have all been associated with more severe fibrosis in HCV. Again, an important observation is that the onset of insulin resistance occurs early, before the development of cirrhosis.\textsuperscript{56}

The effect of type 2 diabetes on the histologic severity of alcoholic liver disease has not been widely studied. Raynard et al\textsuperscript{57} showed that obesity and increased fasting glucose levels were associated with increased severity of hepatic fibrosis in alcoholic liver disease, independently of daily alcohol intake and duration of alcohol abuse.\textsuperscript{57} Although the prevalence of type 2 diabetes was not reported in this study, the link with elevated serum glucose suggests that type 2 diabetes may also be correlated with more severe disease.

TYPE 2 DIABETES AND COMPLICATIONS OF LIVER CIRRHOSIS

Type 2 diabetes seems to be associated with an increased risk of cirrhosis complications. The Verona Diabetes Study, a population-based study on more than 7000 subjects with type 2 diabetes, found an increased risk of death from chronic liver disease and cirrhosis compared with the general population (standardized mortality ratio after 5 years of 2.52, 95\% confidence interval [CI], 1.96-3.2).\textsuperscript{58} In addition, there was an increased risk of mortality from hepatocellular carcinoma (standardized mortality ratio after 10 years of 1.86, 95\% CI, 1.43-2.38).\textsuperscript{58} Insulin treatment of type 2 diabetes, perhaps as a marker of more severe diabetes, was associated with a particularly high risk of mortality in cirrhotic patients (relative risk 6.84).\textsuperscript{59}
Similar observations have been made in smaller cohort studies. Younossi et al. found that in nonalcoholic fatty liver disease, patients with type 2 diabetes had an overall mortality twice that of nondiabetic subjects. After adjustment for potential confounders, including cirrhosis, the risk ratio was 22.83 (95% CI, 2.97-175.03) for liver-related mortality in those with type 2 diabetes and 3.30 (95% CI, 1.76-6.18) for overall mortality. Nishida et al. also found that the survival rates of cirrhotic patients with type 2 diabetes were significantly lower than those with normal glucose tolerance.

Several studies have demonstrated an increased incidence of diabetes among patients with hepatocellular carcinoma ranging from 2- to 4-fold. Type 2 diabetes seems to play an etiologic role in hepatocellular carcinoma cirrhosis independently of alcohol, viral hepatitis, or demographic features, although the risk of hepatocellular carcinoma increases up to 10-fold when viral hepatitis and hazardous alcohol consumption are combined with type 2 diabetes.

**HOW MIGHT TYPE 2 DIABETES MELLITUS MAKE LIVER DISEASE WORSE?**

The pathogenic mechanisms underlying the relationship between type 2 diabetes and chronic liver disease remain to be elucidated. Generalized peripheral insulin resistance and altered β-cell function are usually present. The role of increased proinflammatory cytokines, reduction in protective cytokines, hyperinsulinemia and hyperglycemia in the activation of hepatic stellate cells, and stimulation of collagen production are prime focuses of research in this area.

There seems to be cross-talk between adipose tissue and other tissues mediated in part by the release of cytokines from adipose tissue, known collectively as adipokines. Adipokines, such as leptin and tumor necrosis factor-α, activate inflammatory pathways that may exacerbate liver injury.

The serum concentration of most adipokines is increased in obesity and type 2 diabetes. An exception to this is adiponectin, a key regulator of insulin sensitivity and tissue inflammation. Plasma concentrations of adiponectin and hepatic adiponectin receptor expression are reduced in nonalcoholic fatty liver disease, and it has been hypothesized that hypoadiponectinemia may play a role in disease progression. Xu et al. demonstrated a potent protective effect of adiponectin in animal models of both alcoholic liver disease and nonalcoholic fatty liver disease. Administration of recombinant adiponectin to a mouse model of alcoholic liver disease reduced hepatic steatosis and significantly reduced hepatic inflammation and serum alanine aminotransferase. Adiponectin had similar effects in the ob/ob mouse model of nonalcoholic fatty liver disease. To date, studies in humans of the role of adiponectin in liver disease have produced conflicting results, with some studies reporting a protective effect against hepatic steatosis, necroinflammation, and fibrosis, and others reporting no correlation with disease severity. Data regarding a link among adiponectin, steatosis, and disease progression in chronic HCV are emerging with evidence of genotype-specific interactions with adiponectin.

Insulin stimulates the proliferation of hepatic stellate cells and induces production of collagen, resulting in hepatic fibrosis. Connective tissue growth factor is produced by activated hepatic stellate cells and has been implicated in the development and progression of hepatic fibrogenesis. Hyperglycemia and hyperinsulinemia stimulate connective tissue growth factor synthesis in hepatic stellate cell cultures, and connective tissue growth factor has been found to be overexpressed in liver tissue from patients with nonalcoholic steatohepatitis.

**SIGNIFICANCE**

Patients with type 2 diabetes seem more likely to have a range of liver diseases, and patients with liver disease and diabetes are at risk of severe liver disease, cirrhosis, liver failure, and hepatocellular carcinoma. This has obvious implications for the clinical management. The increasing incidence of obesity and type 2 diabetes in children means we may see more severe chronic liver disease occurring at younger ages. Awareness of type 2 diabetes as a significant risk factor for liver injury may improve diagnosis and interventions to minimize the progression of chronic liver disease.

Our understanding of the links between type 2 diabetes and the development and progression of chronic liver disease has benefited from the mainly retrospective studies performed to date, but prospective studies are needed to fully elucidate the cause and effect of type 2 diabetes in liver injury. Identifying the mechanisms whereby type 2 diabetes increases disease severity could offer new insights into the treatment of chronic liver disease, including the role of weight reduction and pharmacologic interventions with insulin sensitizers.

**CONCLUSIONS**

Type 2 diabetes is prevalent in a range of liver diseases, particularly nonalcoholic fatty liver disease, chronic HCV, hemochromatosis, and alcoholic liver disease. Coexistent type 2 diabetes seems to be associated with more severe liver injury before the onset of cirrhosis and more severe complications and higher mortality once cirrhosis is established. There is evidence that the metabolic disturbances associated with type 2 diabetes contribute to liver injury, but this relationship is made more complex by the association of cirrhosis with hepatogenous diabetes. It is unclear whether treatment of coexistent diabetes and improved glycemic control will benefit chronic liver disease. Clinicians should be aware that patients with type 2 diabetes may have underlying chronic liver disease. In the setting of type 2 diabetes and cirrhosis, consideration should be given to surveillance for life-threatening complications of liver disease, such as hepatocellular carcinoma. A better understanding of the factors that modulate liver disease progression is
critical to identify patients who require more aggressive monitoring, lifestyle interventions, and pharmacotherapy.

References


Considerations for the Diagnosis and Treatment of Testosterone Deficiency in Elderly Men

Mohammed Kazi, MD,a,b Stephen A. Geraci, MD,a,b Christian A. Koch, MD, PhDb

aMedical Service, G.V. (Sonny) Montgomery Veterans Affairs Medical Center, Jackson, Miss, bDepartment of Medicine, University of Mississippi Medical Center, Jackson.

ABSTRACT

Increased longevity and population aging will increase the number of men with relative testosterone deficiency, as systemic levels of testosterone decrease by about 1% each year. Androgen deficiency should only be diagnosed in men with definite signs and symptoms, accompanied by low total testosterone levels measured in the morning by a reliable assay. Although clinical trials data are limited, current practice guidelines recommend testosterone replacement therapy for symptomatic men with low testosterone levels to improve bone mineral density, muscle mass and strength, sexual function, and quality of life. Testosterone replacement is not recommended for all older men with low testosterone levels, and should be avoided in patients with prostate or breast cancer, hyperviscosity, erythrocytosis, untreated obstructive sleep apnea, or severe heart failure. The goal of all available testosterone treatment modalities (intramuscular injections, nongenital patch or gel, bioadhesive buccal and oral testosterone, and pellets) is to achieve serum testosterone levels in the mid-normal range during treatment. Cost varies widely among these preparations and may limit their use. Patients receiving testosterone replacement therapy should be re-evaluated 3 months after testosterone initiation and at least annually thereafter. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Elderly; Hypogonadism; Testosterone; Therapy

Male hypogonadism is defined as failure of the testes to produce normal amounts of testosterone, combined with signs and symptoms of androgen deficiency. Systemic testosterone levels fall by about 1% each year in men. Therefore, with increasing longevity and the aging of the population, the number of older men with testosterone deficiency will increase substantially over the next several decades.1-4 The goal of this article is to provide the primary care physician with guidelines for diagnosing and treating testosterone deficiency in the elderly outpatient population. However, it must be emphasized that treatment of testosterone deficiency in older men is controversial due to the lack of outcomes data from large scale clinical trials. Recommendations in this article are therefore based on recent clinical practice guidelines developed by the Endocrine Society.5

Serum testosterone levels decrease progressively in aging men, but the rate and magnitude of decrease vary considerably. Approximately 1% of healthy young men have total serum testosterone levels below 250 ng/dL; in contrast, approximately 20% of healthy men over age 60 years have serum testosterone levels below this value.6-8 The Baltimore Longitudinal Study on Aging reported an average annual decrease of total serum testosterone of 3.2 ng/dL in men older than 53 years (ie, about 1% per year based on a lower limit of normal of 325 ng/dL).9 According to the Massachusetts Male Aging Study, sex-hormone-binding globulin (SHBG) increases by 1.2% annually. This is important because most circulating testosterone is bound to SHBG or to albumin. Therefore, free and bioavailable testosterone levels decrease with age to a greater degree than is reflected by the total testosterone level. However, free and bioavailable testosterone levels can be calcu-
lated from total testosterone, SHBG, and serum albumin concentrations (http://www.issam.ch/freetesto.htm).9

ETIOLOGY OF MALE HYPOGONADISM
Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels decrease with age in healthy men. For this reason, the most common cause of androgen deficiency in elderly men is hypogonadotropic hypogonadism (ie, inappropriately low/normal LH and FSH related to pituitary or hypothalamic insufficiency). In addition, Leydig cell function in the testes decreases with aging and is affected by several medications, including glucocorticoids, spironolactone, opiates, and ketoconazole. Neuroleptic drugs that cause hyperprolactinemia can inhibit the release of gonadotropin-releasing hormone, leading to hypogonadotropic hypogonadism.2,5

Medical conditions associated with a high prevalence of low testosterone levels include type 2 diabetes mellitus, end-stage renal disease, osteoporosis or low-trauma fracture, infertility, diseases of the sellar region, weight loss due to malignancy or human immunodeficiency virus (HIV), and other less common chronic disorders.5

DIAGNOSIS OF MALE HYPOGONADISM
Several questionnaires have been developed to assess symptoms of androgen deficiency (Table 1), but it is essential to distinguish this condition from major depressive disorder, with which there is substantial symptomatic overlap.6,10,11 Other findings suggestive of testosterone deficiency in men include hot flashes and diaphoresis, very small or shrinking testes (adult testes are usually about 4.5 cm × 2.8 cm), reduced need for shaving, breast discomfort and gynecomastia, decreased spontaneous erections, reduced sexual desire and activity, reduced muscle bulk and strength, inability to father children (due to low or zero sperm counts), height loss, low bone mineral density, and low-trauma fractures. Less specific findings include decreased energy, depressed mood, mild anemia, and diminished physical or work performance.5,12

Measuring serum testosterone levels in the general population to screen for androgen deficiency is not recommended. However, in older men with clinical symptoms and signs consistent with androgen deficiency, the Endocrine Society recommends measuring a mid-morning total serum testosterone level using a reliable assay (Figure). When measuring serum testosterone, several factors need to be considered. Peak testosterone levels occur between 7 and 10 AM. Diet does not significantly affect the serum testosterone level, but a high insulin level (eg, following a high carbohydrate meal) can lower SHBG. Heavy alcohol consumption can decrease serum testosterone. On average, smokers have total and free testosterone levels 5%-15% higher than nonsmokers. SHBG levels are decreased in moderate obesity, hypothyroidism, glucocorticoid use, and nephrotic syndrome, and increased in hyperthyroidism, anticonvulsant use, cirrhosis, and other conditions (Table 2).5

Local laboratories usually cannot reliably or accurately measure free serum testosterone. However, free and bioavailable testosterone can be calculated from total testosterone, SHBG, and albumin (http://www.issam.ch/freetesto.htm).9 Approximately 2% of serum testosterone is unbound or free. Because testosterone can rapidly dissociate from albumin, all non-SHBG-bound testosterone is considered bioavailable. For total testosterone, the lower limit of the normal range is considered to be around 315 ng/dL (11 nmol/L); for free testosterone and bioavailable testosterone, lower limits of normal are around 6.5 ng/dL and 140 ng/dL, respectively.2 The “free testosterone index” is obtained by dividing the total testosterone level (in nanomoles per liter) by the SHBG concentration (in nanomoles per liter), but this is not a valid measure of free testosterone in older men.

If the initial total testosterone level is low (<300 ng/dL or 10.4 nmol/L, or below the lower limit of normal for healthy young men according to the reference range of the local laboratory), the measurement should be repeated, as 30% of men with an initially low level will have a normal level upon repeat testing. Conversely, men with true deficiency states demonstrate persistently low testosterone levels. In addition, LH and FSH levels should be measured, because secondary hypogonadism is a common cause of androgen deficiency in older men (Figure). If total testosterone, LH, and FSH are low, measurement of other anterior pituitary hormones (eg, prolactin) and perhaps a magnetic resonance scan of the pituitary should be considered to exclude intra-and perisellar lesions.

A recent cross-sectional analysis in 2 independent populations of healthy men (Belstress study, consisting of 2322 men aged 35 to 59 years; and Siblos study, consisting of 358 men aged 25 to 45 years) showed androgen receptor polyglutamine tract polymorphism encoded by a CAG repeat of variable length in exon 1 of the AR gene might play an important role in subject variability in serum (free) testosterone in healthy men because of differences in androgen sensitivity and feedback (LH) setpoint. CAG repeat length

<table>
<thead>
<tr>
<th>Table 1 Testosterone Deficiency in Aging Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are your erections less strong?</td>
</tr>
<tr>
<td>2. Do you have a decrease in libido (sex drive)?</td>
</tr>
<tr>
<td>3. Do you have a lack of energy?</td>
</tr>
<tr>
<td>4. Are you falling asleep after dinner?</td>
</tr>
<tr>
<td>5. Has there been a recent deterioration in your work performance?</td>
</tr>
<tr>
<td>6. Have you noticed a decreased enjoyment of life?</td>
</tr>
<tr>
<td>7. Do you have decrease in strength and/or endurance?</td>
</tr>
<tr>
<td>8. Have you noted a recent deterioration in your ability to play sports?</td>
</tr>
<tr>
<td>9. Are you sad and/or grumpy?</td>
</tr>
<tr>
<td>10. Have you lost weight?</td>
</tr>
<tr>
<td>Positive test: if the answer is yes to question 1 or 2, or to any 3 other questions</td>
</tr>
</tbody>
</table>

was positively associated with serum total testosterone in both study populations. Increased CAG repeat length was associated with increased free testosterone levels.13

THERAPY

In older men, the testosterone level below which testosterone replacement therapy is recommended is controversial; some experts favor treating symptomatic men with testosterone levels below 300 ng/dL, whereas others favor a threshold of 200 ng/dL.5 In either case, for men with classical androgen deficiency signs and symptoms accompanied by persistently low testosterone levels, testosterone replacement therapy is recommended to improve sexual function, bone mineral density, and sense of well-being, and to induce and maintain secondary sex characteristics.5,12,14,15 Testosterone also is suggested for men with low testosterone levels and erectile dysfunction (ED) after other causes of ED have been excluded.12 Short-term adjunctive therapy with testosterone may be considered in HIV-infected men with low testosterone levels and weight loss to improve muscle strength and promote weight gain. Testosterone also should be considered in men with low testosterone levels who are receiving high dose glucocorticoid therapy in order to help preserve bone mineral density.

Improved sexual activity scores and increased duration and frequency of nocturnal erections result from effective testosterone therapy in young hypogonadal men,4 but data are limited in older men, among whom the association between androgens and sexual function is more controversial.5,16 Dose-dependent increases in hemoglobin concentration and in bone mineral density are typically seen with testosterone therapy.17,18 The cardiovascular effects of tes-
testosterone replacement appear to be neutral or mildly benefi-
cial in young men; in older men, there is no convincing
evidence that testosterone therapy is either beneficial or
harmful to the cardiovascular system. Testosterone has
minimal effect on serum lipids, whereas the effect on insulin
sensitivity is controversial.

Hormone-dependent malignancies, such as prostate and
breast cancer, may grow faster during testosterone therapy.
Therefore, testosterone replacement is not recommended in
such patients. It also is not recommended in patients with a
palpable prostate nodule, a prostate-specific antigen (PSA)
>3 ng/mL (pending further urological evaluation), hyper-
viscosity, erythrocytosis (hematocrit >50%), untreated ob-
structive sleep apnea, severe benign prostatic hyperplasia,
or decompensated heart failure. Additional factors that may
influence the decision to initiate testosterone therapy in
older men include functional status and the presence of
cognitive dysfunction. For example, a man who is bedrid-
den is unlikely to benefit from testosterone administered to
improve muscle strength. Importantly, the uncertainties
about the benefits and risks of testosterone should be dis-
cussed with older men on an individualized basis before
embarking on a course of testosterone therapy.

The goal of testosterone therapy is to achieve a serum
testosterone level in the mid-normal range during treatment.
Several formulations and therapeutic regimens are available,
and selection should be based on patient preference,
pharmacokinetics, and cost (Table 3). Testosterone enan-
thane or cypionate is administered intramuscularly, weekly
at a dose of 100 mg, or biweekly at 200 mg. Alternatively,
a 5- or 10-mg nongenital testosterone patch can be applied
to the skin (away from pressure areas) each night. Newer
preparations include testosterone gel applied daily to non-
genital skin (5- to 10-g dose), and bioadhesive testosterone
tablets (30 mg) applied to the to buccal mucosa every 12
hours. In some countries, oral testosterone undecanoate,
injectable testosterone undecanoate, and testosterone pellets
are available. Testosterone doses are generally lower in
older than in younger men because testosterone is metabo-
lized more slowly in the elderly.

After therapy is initiated, the patient should be re-eval-
uated at 3 months and at least annually thereafter. Special
attention should be directed to symptoms before and after
treatment to determine whether there has been a satisfactory
response and to assess for adverse effects. A mid-morning
total serum testosterone level should be obtained, with a
target range of 350-700 ng/mL (12.3-24.5 nmol/L); for
older men, a range of 400-500 ng/dL (14.0-17.5 nmol/L) is
suggested. For injectable testosterone, the serum level
should be measured between injections. For men treated
with a transdermal testosterone patch, the serum level
should be measured 3 to 12 hours after patch application.
In patients receiving buccal testosterone tablets, the serum
level should be measured immediately before application of
a fresh system. Patients on testosterone gel may have levels
checked anytime after at least 1 week of therapy.

The hematocrit should be measured at baseline, at 3
months, and annually thereafter. If the hematocrit exceeds
54%, testosterone therapy should be discontinued. Digital
rectal examination and PSA measurement should be per-
formed before starting testosterone therapy. If the PSA
increases above 4 ng/mL, or by more than 1.4 ng/mL within
12 months of treatment, urological consultation should be
obtained.

Patients on testosterone replacement should be evalu-
ated for adverse drug effects specific to each preparation.
These include excessive erythrocytosis and fluctuations
in mood or libido (injectable testosterone); skin reactions
(patch); and alterations in taste and gum irritation (buccal
testosterone).

SUMMARY

Aging in healthy men is associated with a decrease in
serum testosterone levels. Clinically significant androgen
deficiency in older men is most often related to pituitary
or hypothalamic abnormalities rather than to primary
testicular failure. The challenge in diagnosing androgen
deficiency in the elderly is to link signs and symptoms to
serum testosterone levels. Questionnaires for assessing
symptoms of testosterone deficiency in the aging male
have been developed, and these instruments also may be
helpful in evaluating for depression. Measuring serum
testosterone levels accurately and reliably is problematic,
amid measurement issues must be taken into consideration
when making a diagnosis of testosterone deficiency in an
elderly man. Total serum testosterone should be mea-
sured in the morning in a man with signs and symptoms
consistent with androgen deficiency. If low, the measure-
ment should be repeated to confirm the diagnosis, be-
cause there is a 30% “false positive” rate with initial
screening. LH and FSH also should be measured to dis-
tinguish primary from secondary hypogonadism.

Although data from large scale clinical trials in elderly
men are lacking, testosterone replacement therapy is rec-
ommended in men with definite symptoms and signs of
androgen deficiency in conjunction with a persistently low
serum testosterone level. Several testosterone preparations
are available, and selection of a therapeutic modality should
be based on considerations of personal preference, side
effect profile, pharmacokinetics, and cost. In addition, fac-
tors such as functional status and cognitive impairment may
influence the decision to treat and the choice of therapy in
older men. Following initiation of treatment, re-evaluation
for efficacy and side effects should be performed after 3
months of therapy and at least annually thereafter. Finally,
given the anticipated increase in the number of older men
with androgen deficiency, there is a compelling need for
additional research, including large scale clinical trials, to
determine the short- and long-term benefits and risks of
testosterone replacement therapy.
<table>
<thead>
<tr>
<th>Formulation</th>
<th>Replacement Dosage</th>
<th>Approximate Cost</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td><strong>T esters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T enanthate or cypionate</td>
<td>100 mg/wk IM or 200 mg q 2 wk IM</td>
<td><strong>$70/month</strong>&lt;br&gt;(200 mg per 2 weeks)</td>
<td>Extensive clinical experience&lt;br&gt;Inexpensive</td>
</tr>
<tr>
<td></td>
<td>Injectable long-acting T undecanoate in oil</td>
<td>1000 mg IM, then 1000 mg at 6 wk, and 1000 mg every 12 wk</td>
<td>Not available in the US</td>
<td>Corrects symptoms of androgen deficiency&lt;br&gt;Requires less frequent administration</td>
</tr>
<tr>
<td></td>
<td>Nongenital transdermal T patch</td>
<td>5 mg, 1-2 patches every night applied to nonpressure areas (thigh, arm)</td>
<td><strong>$192/month</strong>&lt;br&gt;(5 mg/d)</td>
<td>Physiological circadian T levels, no injection, Good adhesion, normal DHT levels</td>
</tr>
<tr>
<td></td>
<td>Scrotal T patch</td>
<td>6 mg over 24 h applied daily</td>
<td><strong>$131 for 30 patches</strong></td>
<td>Symptoms of androgen deficiency are corrected&lt;br&gt;Physiological T levels, Little skin irritation&lt;br&gt;Dose flexibility, Musk odor</td>
</tr>
<tr>
<td></td>
<td>T gels</td>
<td>5-10 gm every AM</td>
<td><strong>$205-248/month</strong>&lt;br&gt;(5 g/d)</td>
<td>Steady-state T levels, No hand washing&lt;br&gt;Dose flexibility, Musk odor</td>
</tr>
<tr>
<td></td>
<td>Buccal T tablets bioadhesive T pellets</td>
<td>30 mg every 12 h</td>
<td><strong>$190/month</strong></td>
<td>Symptoms of androgen deficiency are corrected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-6 200 mg pellets implanted SC</td>
<td><strong>$150 per 10 pellets</strong></td>
<td></td>
</tr>
</tbody>
</table>

RESOURCES
http://www.hormone.org/public/factsheets.cfm
http://www.endo-society.org/quickcontent/clinicalpractice/clinical-guidelines/CG_Androgen.cfm
http://www.aace.com/pub/guidelines/
http://www.issam.ch/freetesto.htm


ACKNOWLEDGMENT
We wish to thank Dr. William C. Nicholas for critical review of this manuscript.

References
Orthostatic Hypotension in the Elderly: Diagnosis and Treatment

Vishal Gupta, MD, PhD, Lewis A. Lipsitz, MD
Beth Israel Deaconess Medical Center, Hebrew SeniorLife, and Harvard Medical School, Boston, Mass.

ABSTRACT

Orthostatic hypotension is a common problem among elderly patients, associated with significant morbidity and mortality. While acute orthostatic hypotension is usually secondary to medication, fluid or blood loss, or adrenal insufficiency, chronic orthostatic hypotension is frequently due to altered blood pressure regulatory mechanisms and autonomic dysfunction. The diagnostic evaluation requires a comprehensive history including symptoms of autonomic nervous system dysfunction, careful blood pressure measurement at various times of the day and after meals or medications, and laboratory studies. Laboratory investigation and imaging studies should be based upon the initial findings with emphasis on excluding diagnoses of neurodegenerative diseases, amyloidosis, diabetes, anemia, and vitamin deficiency as the cause. Whereas asymptomatic patients usually need no treatment, those with symptoms often benefit from a stepped approach with initial nonpharmacological interventions, including avoidance of potentially hypotensive medications and use of physical counter maneuvers. If these measures prove inadequate and the patient remains persistently symptomatic, various pharmacotherapeutic agents can be added, including fludrocortisone, midodrine, and nonsteroidal anti-inflammatory drugs. The goals of treatment are to improve symptoms and to make the patient as ambulatory as possible rather than trying to achieve arbitrary blood pressure goals. With proper evaluation and management, the occurrence of adverse events, including falls, fracture, functional decline, and myocardial ischemia, can be significantly reduced. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Aging; Blood pressure; Elderly; Office practice; Orthostatic hypotension

EPIDEMIOLOGY

In 1995, the American Academy of Neurology and the Joint Consensus Committee of the American Autonomic Society defined orthostatic hypotension as a reduction in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 minutes of assuming an erect posture. This definition does not account for a fall in blood pressure after 3 minutes or symptoms associated with smaller decreases in blood pressure upon standing. Hence, the significance of any decrease in blood pressure upon standing should be evaluated according to its association with symptoms of dizziness, presyncope, syncope, or falls.

Requests for reprints should be addressed to Lewis A. Lipsitz, MD, Hebrew SeniorLife, Institute for Aging Research, 1200 Centre Street, Boston, MA 02131.
E-mail address: lipsitz@hrca.harvard.edu

© 2007 Elsevier Inc. All rights reserved.
PATHOGENESIS

In healthy people, approximately 500 to 1000 milliliters of blood is transferred below the diaphragm upon assuming an erect posture. This leads to decreased venous return to the heart, reduced ventricular filling, and a transient decrease in cardiac output and blood pressure. As a consequence, baroreceptors in the carotid arteries and aorta are activated, resulting in increased sympathetic outflow and decreased parasympathetic outflow from the central nervous system. This compensatory reflex restores cardiac output and blood pressure by increasing heart rate and vascular resistance.

Blood pressure varies directly with heart rate, stroke volume, and vascular resistance. Therefore, impairments in the response of any of these parameters during postural change may result in orthostatic hypotension. As shown in Table 1, aging is associated with a decrease in baroreflex sensitivity, which manifests as a diminished heart rate response and α-1-adrenergic vasoconstrictor response to sympathetic activation. Also, an age-related reduction in parasympathetic tone results in less cardioacceleration during the vagal withdrawal that normally occurs with standing. Due to reductions in renin, angiotensin, and aldosterone with aging, and an elevation in natriuretic peptides, the aged kidney loses some of its ability to conserve salt and water during periods of fluid restriction or volume loss, leading to rapid dehydration. In addition, the aged heart becomes stiff and non-compliant, resulting in impaired diastolic filling. This reduces stroke volume when preload is decreased due to standing or volume contraction.

Taken together, the reductions in baroreflex-mediated cardioacceleration and vasoconstriction, renal salt and water conservation, and cardiac filling greatly increase the risk of hypotension in the elderly. Severe, symptomatic orthostatic hypotension may develop in the face of any additional stress that lowers blood pressure or impairs the compensatory response, including certain medications, reduced intravascular volume, or other situations that reduce cardiac preload.

ETIOLOGY

Causes of orthostatic hypotension can be broadly divided into acute and chronic (Figure 1). Acute orthostatic hypotension most commonly develops over a relatively short period of time and is more often symptomatic at the outset. Generally, it results from acute conditions such as adrenal insufficiency, myocardial ischemia, medication administration, sepsis, or dehydration. In contrast, chronic orthostatic hypotension develops gradually over a prolonged period of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Age-Related Changes that Can Affect Normal Blood Pressure Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased baroreflex sensitivity</td>
<td></td>
</tr>
<tr>
<td>Decreased α-1-adrenergic vasoconstrictor response to sympathetic stimuli</td>
<td></td>
</tr>
<tr>
<td>Decreased parasympathetic activity</td>
<td></td>
</tr>
<tr>
<td>Decreased renal salt and water conservation</td>
<td></td>
</tr>
<tr>
<td>Increased vascular stiffness</td>
<td></td>
</tr>
<tr>
<td>Reduced left ventricular diastolic filling</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 Etiology of orthostatic hypotension (OH).
time and the patient is usually asymptomatic during the initial period. Chronic orthostatic hypotension can be due to either physiologic or pathologic causes. Physiologic causes are those attributable to the age-associated changes in blood pressure regulation described above, as well as the age-related increase in systolic blood pressure, which further impairs adaptive responses to hypotensive stresses. These physiologic changes predispose elderly people to symptomatic hypotension in the face of common everyday stresses, such as posture change, meals, new medications, fluid restriction, or any acute illness. Pathologic causes of chronic orthostatic hypotension are secondary to central or peripheral nervous system diseases that result in autonomic insufficiency (Figure 1).

CLINICAL FEATURES
Orthostatic hypotension may be symptomatic or asymptomatic. However, even in asymptomatic patients it remains a risk for future falls and syncope, and should therefore be minimized as much as possible. Common symptoms at all ages include dizziness, light headedness, weakness, syncope, nausea, paracervical pain, low back pain, angina pectoris, and transient ischemic attacks. In elderly people, disturbed speech, visual changes, falls, confusion, and impaired cognition are more commonly seen. However, the predictive value of these symptoms in the elderly is poor, due to intake of multiple medications with various side effects and overlapping symptoms arising from comorbid conditions. Therefore, careful blood pressure measurements are of critical importance, even in patients with atypical symptoms.

EVALUATION
Our approach to the evaluation of orthostatic hypotension is shown in Figure 2. Initial evaluation should include measuring blood pressure and heart rate after the patient has been quietly supine for at least 5 minutes and again after 1 minute and 3 minutes of standing. Early morning measurements, especially after a high carbohydrate meal, are useful to identify postprandial hypotension. Although postprandial hypotension may occur concomitantly with orthostatic hypotension, it is a distinct entity that often occurs while sitting after a meal, and may actually resolve upon standing up and walking. Detection of orthostatic hypotension may

---

**Figure 2** Approach to the evaluation of orthostatic hypotension. BMP = basic metabolic profile; CBC = complete blood count; CT = computerized tomography; H&P = history and physical examination; MRI = magnetic resonance imaging; RPR = rapid plasma reagin.
require multiple measurements on different days. This can be accomplished with ambulatory blood pressure monitoring, or by loaning the patient an automatic blood pressure monitor with instructions to maintain a diary with recordings of supine and standing blood pressure at different times of the day for several days. Measurements before breakfast, after medications, after meals, and before bed are most useful. Furthermore, the heart rate response to postural change can provide important clues to the etiology. Minimal heart rate acceleration (<10 beats per minute) on standing from a supine position in the presence of hypotension suggests baroreflex impairment, whereas tachycardia (>20 beats per minute) indicates volume depletion or orthostatic intolerance. Note, however, that lack of tachycardia also may occur in volume-depleted elderly patients due to baroreflex impairment.

Once the diagnosis of orthostatic hypotension is established, a detailed history should be obtained, focusing on medications (both prescription and nonprescription), volume losses (vomiting, diarrhea, fluid restriction), coexisting medical disorders, and autonomic dysfunction. A comprehensive physical examination should be performed, seeking clinical clues to possible underlying physiological and pathological disorders (Table 2). These include signs of amyloidosis, malignancy, and heart failure. A neurological evaluation should include a mental status examination (to identify neurodegenerative diseases such as Lewy Body Dementia), motor testing (Parkinson’s disease or multiple strokes), sensory testing (peripheral neuropathy), and pupillary size (Horner’s syndrome). Subsequent laboratory tests should be obtained based on the results of these assessments. These may include hemoglobin and hematocrit levels to evaluate for anemia; blood electrolytes, urea nitrogen, and creatinine to assess for dehydration; a rapid plasma reagin (RPR) test for syphilis; and a glucose tolerance test for diabetes. Brain imaging studies should be ordered if clinical suspicion points towards central nervous system pathology.

Autonomic function testing is helpful when the history and physical examination are equivocal, to evaluate the extent of autonomic involvement, and to monitor the course of an autonomic disorder and its response to therapy. Commonly used bedside studies to assess autonomic function are heart rate variation in response to deep breathing (respiratory sinus arrhythmia) and blood pressure response to the cold pressor test. Heart rate variation during deep breathing assesses the function of parasympathetic (vagal) efferents to the heart. Sinus arrhythmia is measured by electrocardiography with the patient lying supine during 1 minute of slow and deep breathing with 5 seconds inspiration and 7 seconds expiration. In healthy elderly people, the ratio of longest expiratory R-R interval to shortest inspiratory R-R interval is >1.15. Potential confounders that may reduce heart rate variability include medications (beta-blockers, calcium channel blockers, anticholinergic agents), advanced age, the patient’s position (sitting vs. supine), and hypocapnia. The cold pressor test evaluates sympathetic innervation of the vasculature. After immersion of one hand in ice cold water at 4°C for 1 minute, a normal response is a systolic blood pressure elevation ≥15 mm Hg and diastolic elevation ≥10 mm Hg. Other tests that can be considered include plasma norepinephrine and vasopressin levels supine and upright to distinguish central from peripheral causes of autonomic failure. In central causes, supine norepinephrine is normal but fails to increase with postural change, and vasopressin is low. In peripheral causes, supine norepinephrine levels are low and vasopressin is normal. However, in practice the high variability of these levels undermines their utility.

**MANAGEMENT**

Due to the presence of multiple co-morbid conditions and nonspecific signs and symptoms, treatment of orthostatic

---

**Table 2** Additional Clinical Clues and Tests to Order

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Possible Etiology</th>
<th>Test to Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecchymoses, purpura, macroglossia, numbness, paresthesias, pseudohypertrophy of muscle</td>
<td>Amyloidosis</td>
<td>Rectal biopsy</td>
</tr>
<tr>
<td>Diarrhea, vomiting, burns, fever</td>
<td>Volume depletion</td>
<td>Electrolytes, BUN, Creatinine</td>
</tr>
<tr>
<td>Gummas, unequal pupils (Argyll Robertson pupil) loss of position and vibration senses, history of sexually transmitted disease</td>
<td>Tabes dorsalis</td>
<td>RPR, VDRL</td>
</tr>
<tr>
<td>Early satiety, postprandial fullness, constipation, incontinence, exercise intolerance</td>
<td>Diabetic neuropathy</td>
<td>EKG for deep breath variability, GTT</td>
</tr>
<tr>
<td>Chest pain, palpitation, shortness of breath, pedal edema</td>
<td>Cardiogenic causes</td>
<td>EKG, echocardiogram</td>
</tr>
<tr>
<td>Reduced sweating, incontinence, constipation, posture</td>
<td>Multiple system atrophy</td>
<td>Autonomic testing</td>
</tr>
<tr>
<td>difficulties, tremors, rigidity</td>
<td>Alcoholic neuropathy</td>
<td>CBC, random alcohol level</td>
</tr>
<tr>
<td>Confusion, cerebellar symptoms, nystagmus, amnesia, confabulation, history of alcohol abuse</td>
<td>Pernicious anemia</td>
<td>CBC, cobalamin level, folate level</td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen; CBC = complete blood count; EKG = electrocardiogram; GTT = glucose tolerance test; RPR = rapid plasma reagin; VDRL = venereal disease research laboratory.
hypotension in the elderly is often challenging. Instead of aiming to achieve arbitrary blood pressure goals, the treatment of orthostatic hypotension should be directed toward ameliorating symptoms, correcting any underlying cause, improving the patient’s functional status, and reducing the risk of complications. Broadly, interventions can be divided into nonpharmacological and pharmacological approaches.

Nonpharmacological Interventions
Generally it is best to start with nonpharmacological interventions and, if this fails, then proceed to drug therapy (Table 3). The first management step involves removing any medication that could precipitate orthostatic hypotension. Common offending drugs include nitrates, tricyclic antidepressants, neuroleptics, and alpha-blockers (often used for urinary frequency or retention). Orthostatic hypotension may develop when a patient begins taking an anti-hypertensive medication, but it may improve with continued use.6 Therefore, it is imperative to start with a low dose and slowly titrate the dose upward. In patients with acute orthostatic hypotension due to dehydration, fluid replacement therapy should be initiated. Patients who have had prolonged bedrest or inactivity (eg, following hospitalization) should be instructed to stand up gradually to mitigate excessive pooling of blood in the lower extremities. Activities that decrease venous return to the heart, such as coughing, straining, and prolonged standing, should be avoided, particularly in hot weather. Dorsiflexion of the feet before assuming an upright posture may promote venous return to the heart, accelerate the heart rate, and increase blood pressure. Squatting and stooping forward can result in an increase in blood pressure. In patients who present with symptoms after prolonged standing, simply sitting down can often raise the blood pressure. Physical counter-maneuvers like crossing one’s legs while standing and maintaining muscle contraction for 30 seconds can increase systemic venous return, thereby causing increased cardiac output and blood pressure. Waist high compression stockings and abdominal binders may be helpful. In patients with autonomic failure and supine hypertension, raising the head of the bed by 10 to 20 degrees at night can reduce hypertension, prevent overnight volume loss, and help restore morning blood pressure upon standing. Liberal intake of salt and water to achieve a 24-hour urine volume of 1.5 to 2 liters may attenuate fluid loss commonly seen in autonomic insufficiency. In elderly patients with orthostatic hypotension related to deconditioning, an exercise regimen comprising swimming, recumbent biking, or rowing might lead to disappearance of symptoms.

Pharmacological Interventions
Numerous pharmacological agents are available if the patient remains symptomatic despite the above measures (Table 4). One of the most potent agents is fludrocortisone, a synthetic mineralocorticoid, which has a principal mode of action of reducing salt loss and expanding blood volume.7 The initial dose is 0.1 mg per day with increments of 0.1 mg every week until there is development of trace pedal edema or the maximum dose of 1 mg per day is reached. Common side effects include hypokalemia, supine hypertension, heart failure, and headache. Elderly patients should be monitored for fluid overload and hypokalemia. In patients taking higher doses, potassium supplements are usually required.

If the patient remains symptomatic, midodrine, an alpha-agonist with selective vasopressor properties, is often effective.8 The starting dose is 2.5 mg 3 times per day, and the dose should be titrated upwards in 2.5-mg increments at weekly intervals until a maximum of 10 mg 3 times per day

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Contraindication</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludrocortisone</td>
<td>Initial: 0.1 mg daily Max.: 1 mg daily</td>
<td>Hypersensitivity</td>
<td>Supine hypertension, hypokalemia, HF, headache</td>
</tr>
<tr>
<td>Midodrine</td>
<td>Initial: 2.5 mg tid Max.: 10 mg tid</td>
<td>Severe OHD, urinary retention, thyrotoxicosis, acute renal failure</td>
<td>Supine hypertension, piloerection, pruritus, paresthesia</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400-800 mg tid</td>
<td>Hypersensitivity to NSAIDs, active bleeding, impaired renal function</td>
<td>GI intolerance, bleeding, headache, dizziness, renal insufficiency</td>
</tr>
<tr>
<td>Caffeine</td>
<td>100-250 mg daily</td>
<td>Hypersensitivity</td>
<td>GI irritation, insomnia, agitation, nervousness</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>25-75 U/Kg tiw</td>
<td>Uncontrolled hypertension</td>
<td>Stroke, myocardial infarction, hypertension</td>
</tr>
</tbody>
</table>

GI = gastrointestinal; HF = heart failure; NSAIDs = non-steroidal anti-inflammatory drugs; OHD = organic heart disease.
is achieved. For best results, the morning dose should be given early and the evening dose no later than 6 PM. Combination therapy of fludrocortisone and midodrine using lower doses of both agents (due to synergistic effects) also is beneficial. Adverse effects include supine hypertension, piloerection, pruritus, and paresthesia. Midodrine is contraindicated in patients with coronary heart disease, heart failure, urinary retention, thyrotoxicosis, or acute renal failure. Midodrine should be used cautiously in elderly patients who are taking medications that decrease heart rate, such as beta-blockers, calcium channel blockers, and cardiac glycosides.

Prostaglandin inhibitors, such as indomethacin and other nonsteroidal anti-inflammatory drugs (NSAIDs), can block the vasodilating effects of prostaglandins and raise the blood pressure in some patients with orthostatic hypotension.9 In elderly patients, indomethacin should be avoided because of associated confusion, and all NSAIDs should be used with caution due to gastrointestinal and renal side effects.

The methylxanthine caffeine, administered in a dose of 200 mg every morning as 2 cups of brewed coffee or by tablet, may attenuate symptoms in some patients. Caffeine is an adenosine-receptor blocker that inhibits adenosine-induced vasodilation by blocking these receptors. To avoid tolerance and insomnia, caffeine should not be given more then once in the morning.

Erythropoietin has been shown to be effective in a subgroup of patients with anemia and autonomic dysfunction.10 Although the exact mechanism of action is not known, its effect is probably due to increased red cell mass and blood volume. The principal disadvantage of this drug is the parenteral route of administration. Serious side effects include hypertension, stroke, and myocardial infarction.

Additional pharmacologic agents that may prove useful in selected patients include clonidine and yohimbine. A peripheral α-2-adrenergic agonist, clonidine may improve orthostatic hypotension in patients with central nervous system causes of autonomic failure, in whom there is little or no central sympathetic outflow, by promoting peripheral vasoconstriction and thereby increasing venous return to the heart. Yohimbine is a central α-2-adrenergic antagonist that can increase central sympathetic outflow in some patients with residual sympathetic nervous system efferent output.

**REFERRAL TO A SPECIALIST**

Major indications for referral to a specialist are listed in Table 5. In brief, consultation with a geriatrician should be sought for frail elderly patients, those with multiple comorbid conditions including cognitive decline, failure of standard therapy, any symptom-related complication, or lack of social support. In elderly patients requiring counseling and reinforcement, referral to a geriatrician is beneficial. Adverse effects include supine hypertension, piloerection, pruritus, and paresthesia. Midodrine is contraindicated in patients with coronary heart disease, heart failure, urinary retention, thyrotoxicosis, or acute renal failure. Midodrine should be used cautiously in elderly patients who are taking medications that decrease heart rate, such as beta-blockers, calcium channel blockers, and cardiac glycosides.

### Table 5 Indications for Referral to a Specialist

<table>
<thead>
<tr>
<th>Indications for referral to a geriatrician</th>
<th>Indications for referral to a cardiologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple comorbid conditions</td>
<td>Uncontrolled supine hypertension despite standard therapy</td>
</tr>
<tr>
<td>Failure of standard therapy to alleviate symptoms</td>
<td>Advanced coronary artery disease or severe ischemic symptoms</td>
</tr>
<tr>
<td>Complications, including recurrent falls, fracture, functional decline, ischemic events, decreased quality of life</td>
<td>Severe left ventricular diastolic or systolic dysfunction (ejection fraction &lt; 30%)</td>
</tr>
<tr>
<td>Cognitive decline and confusion</td>
<td>Recent onset of tachy-/bradycardia</td>
</tr>
<tr>
<td>Frail elderly patient &gt;70 years old</td>
<td>Midodrine should be used cautiously in elderly patients who are taking medications that decrease heart rate, such as beta-blockers, calcium channel blockers, and cardiac glycosides.</td>
</tr>
<tr>
<td>Lack of social support</td>
<td>Prostaglandin inhibitors, such as indomethacin and other nonsteroidal anti-inflammatory drugs (NSAIDs), can block the vasodilating effects of prostaglandins and raise the blood pressure in some patients with orthostatic hypotension.</td>
</tr>
</tbody>
</table>

### Table 6 Key Points in Office Management of Orthostatic Hypotension

- Orthostatic hypotension is defined as a reduction in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 minutes of assuming an erect posture. However, the significance of any decrease in blood pressure upon standing should be evaluated in context with associated symptoms.
- Regardless of whether orthostatic hypotension is symptomatic or asymptomatic, the elderly patient remains at significant risk for future falls, fractures, transient ischemic attacks, and myocardial infarction.
- Orthostatic hypotension can be acute or chronic. Acute causes include hypertensive medications, dehydration, and adrenal insufficiency. Chronic causes can be further subdivided into those related to aging or age-related blood pressure elevation (physiologic causes) and those due to central or peripheral autonomic nervous system diseases (pathologic causes).
- The diagnostic evaluation of orthostatic hypotension should include a comprehensive history and physical examination, careful blood pressure measurements, and laboratory studies.
- Goals of treatment in the elderly patient include ameliorating symptoms, correcting any underlying cause, improving the patient’s functional status, and reducing the risk of complications, rather than trying to attain an arbitrary blood pressure goal.
- In most cases, treatment of orthostatic hypotension begins with nonpharmacological interventions, including withdrawal of offending medications (when feasible), physical maneuvers, compression stockings, increased intake of salt and water, and regular exercise.
- If nonpharmacological measures fail to improve symptoms, pharmacologic agents should be initiated. Fludrocortisone, midodrine, nonsteroidal anti-inflammatory drugs, caffeine, and erythropoietin have all been used to treat orthostatic hypotension due to autonomic failure.
can often prove worthwhile when time constraints limit primary care physician effectiveness. Cardiology consultation is indicated for patients with uncontrolled supine hypertension despite standard therapy, advanced symptomatic coronary artery disease, severe heart failure, and in those with recent onset of tachy- or bradyarrhythmias. Referral to a neurologist is suggested primarily for specialized autonomic testing in patients with an unclear diagnosis or progressive autonomic failure.

Key points in the office management of orthostatic hypotension in the elderly are outlined in Table 6.

References
Fact or Factitious?

Stefan Jenni, Beat Gloor, Christoph Stettler, Emanuel R. Christ
Division of Endocrinology, Diabetes, and Clinical Nutrition and Department of Visceral and Transplant Surgery, University Hospital of Bern, Switzerland

PRESENTATION

Psychiatric symptoms may mask a physical problem. Fatigue, stress, disorientation, and lack of concentration lead to an initial diagnosis of depression for this patient, when, in actuality, her underlying condition was something quite different. Our patient, a 36-year-old nurse, was hospitalized in a psychiatric clinic after attempting to commit suicide using regular and isophane insulin combined with benzodiazepines. She was found in a hypoglycemic coma with a capillary glucose level of 3 mmol/L. Blood taken during a subsequent hypoglycemic attack in intensive care revealed a plasma glucose level of 1.8 mmol/L; insulin 11.5 mU/mL; C-peptide 2.5 ng/mL; and a negative sulfonylurea screen. Over 4 days, 1.750 kg of glucose were needed to maintain euglycemia.

She had been in good health until 5 years ago, when she began to suffer from fatigue and difficulty concentrating. Then, about a year ago, she began to experience increasingly frequent bouts of confusion, fatigue, sweating, and trouble with orientation and concentration. At that time, a workup for convulsive disorder revealed a normal electroencephalogram and a normal magnetic resonance (MRI) scan of the brain. Since she also felt stressed and overwhelmed in her job, her general practitioner began treating her for depression.

After the suicide attempt and recovery from coma, she began psychiatric rehabilitation. She was diagnosed with a severe depressive disorder and started taking venlafaxine. She nonetheless continued to suffer from recurring attacks of fatigue, odd behavior, retrograde amnesia, and hypoglycemia. She was eating frequently, even during the night, but assiduously denied further use of insulin or oral antidiabetic agents. As her symptoms disappeared after eating, she was referred for endocrine evaluation.

ASSESSMENT

The patient appeared fully oriented, with a blood pressure of 105/70 mm Hg and a regular pulse of 96 bpm. Her body mass index was 21.7 kg/m² (height 164 cm, weight 58.4 kg). Pulmonary, cardiac, and abdominal examinations were unremarkable, and a fasting test was administered. After 13.25 hours of fasting, she exhibited classic signs of hypoglycemia: neuroglycopenic symptoms (monotone responses, troubles with coordination, inadequate response to simple commands), a low plasma glucose concentration (1.13 mmol/L), and quick recovery (within 10 min) upon intravenous administration of glucose. She remained amnesic for the neuroglycopenic period. Insulin and C-peptide levels were inadequately high, ketone bodies were low, and the sulfonylurea screen was again negative (Table 1).

Abdominal computed tomography (CT) scans revealed 2 lesions in the pancreatic head (Figure 1). In addition, a hypodense structure of 2-cm diameter was found in the body of the pancreas. Two of these lesions were confirmed by endoscopic sonography. At this point, the diagnosis of an insulinoma in the head or body of the pancreas was presumed, and the patient was referred for surgery.

Intraoperatively, sonography of the pancreatic surface confirmed a non-pathologic cyst in the left part of the body of the pancreas. An abnormal vessel in the corpus (which correlated to one of the pancreatic head lesions seen by CT) also was identified. Finally, intraoperative sonography and palpation confirmed the remaining suspect head lesion, which had a diameter of 1.2 cm and was only visible in the CT scan.

DIAGNOSIS

The patient’s hyperinsulinemic hypoglycemia and reactive depression were caused by a single insulinoma in the head of the pancreas. Insulinomas, which are insulin-producing neuroendocrine tumors of the pancreas, occur in about four in 1,000,000 persons. Although most insulinomas are benign and single, 10% are multiple; these are often associated with multiple endocrine neoplasia 1 syndrome.
During the evaluation of hypoglycemic patients, factitious (self-induced) hypoglycemia must always be considered in the differential diagnosis, as this psychiatric illness often mimics the symptoms of insulinoma. Factitious hypoglycemia is particularly likely if psychiatric problems or easy access to glucose-lowering drugs are present. Furthermore, since many patients with factitious disease are healthcare professionals, and most are female, our patient’s symptoms and circumstances initially suggested factitious disease. However, the clear chronology of events in the patient’s history (i.e., appearance of symptoms of hypoglycemia leading to reactive depression and culminating in a suicide attempt with insulin), made factitious hypoglycemia unlikely. The history was confirmed by the results of the fasting test showing neuroglycopenic symptoms in the presence of low glucose concentrations and inadequately raised insulin and C-peptide levels. Exogenous insulin administration was excluded due to the C-peptide concentrations. Furthermore, repeated screenings for sulfonylureas by gas chromatography were negative. (Although it was recently reported that surreptitious use of glinide compounds can cause hypoglycemia, we were prevented from formally excluding glinide abuse by the unavailability of suitable assays.)

In contrast to the common observation that factitious hypoglycemia often mimics insulinoma, our case documents that insulinoma can mimic factitious hypoglycemia. Therefore, a standardized workup is warranted for the patient presenting with hypoglycemia, as a differential diagnosis of factitious disease cannot be assumed even in the case of a healthcare professional with a documented history of insulin abuse and psychiatric illness. Paradoxically, our patient suffered from such severe depression that she attempted suicide with exactly that substance that was responsible for her underlying condition.

**Table 1** Fasting Test

<table>
<thead>
<tr>
<th>Duration of fasting (hours)</th>
<th>Glucose (mmol/l)</th>
<th>Insulin (mU/L)</th>
<th>C-peptide (ng/mL)</th>
<th>γ-hydroxy-butyrate (μmol/L)</th>
<th>Sulfonylurea screen (HPLC)</th>
<th>Neuroglycopenic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.5</td>
<td>1.95</td>
<td>5</td>
<td>1.6</td>
<td>44</td>
<td>negative</td>
<td>++</td>
</tr>
<tr>
<td>13.25</td>
<td>1.13</td>
<td>6.8</td>
<td>2.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plasma glucose: hexokinase method; insulin: microparticle enzyme immunoassay (Abbott Axsym) (normal values < 3 mU/mL in hypoglycemia); C-peptide chemiluminescence: DPC Immulite One (normal values < 0.6 ng/mL in hypoglycemia); sulfonylurea screen: HPLC mass spectroscopy.

**Figure 1** In computed tomography of the pancreas, uptake of contrast medium was noted in the early arterial phase, as shown; it was hypodense in the other phases (not shown).

**Figure 2** Histological detail of the pancreas. A: Hematoxylin & Eosin staining shows cellular proliferations with a trabecularly oriented epithelial pattern, with only small cellular or nuclear atypia, and a solid growth pattern. No infiltration, destructive growth, or angioinvasion was found, and there was no evidence of congophilic deposits. B: Immunohistochemical staining with insulin.

**MANAGEMENT**

The therapeutic strategy for insulinoma consists of resection with minimal damage to the unaffected pancreas. Therefore,
the preferred procedure is enucleation, but if the tumor lies in the cauda, a resection of the pancreatic tail can be performed. Because the patient’s tumor was in close proximity to the main pancreatic duct and the ductus hepato-choledochus, a simple enucleation appeared to be hazardous in this case, and instead a pylorus-preserving duodeno-pancreatectomy was performed. Microscopic and immunohistochemical staining of the resected tumor (Figure 2) confirmed the diagnosis of insulinoma. Thereafter, her blood glucose became normal.

The postoperative course was uneventful, and the patient was transferred to the psychiatric clinic on postoperative day 11. She left the clinic 4 months after her initial admission. During nine months of follow-up care, she has always been free of hypoglycemia, and her endocrine function has been preserved. However, due to a mild exocrine insufficiency, pancreatin substitution is necessary. She is successfully integrated back into her professional and social life.

References
Ischemic ST segment depression occurs frequently during supraventricular tachycardia (SVT), whereas elevation of traditional cardiac injury markers in this setting has rarely been reported. Here, we describe a case of a young man with both ischemic electrocardiographic alterations and markedly elevated troponin associated with rapid SVT and angiographically normal coronary arteries.

PRESENTATION

A 29-year-old man arrived at the emergency department with palpitations that had begun 90 minutes earlier. The palpitations occurred at rest and were associated with shortness of breath, left arm heaviness, and nausea, but no chest discomfort. There was no antecedent illness, and the patient denied use of recreational drugs or over-the-counter medications. His past medical history included similar episodes that had occurred 1–2 times per month since age 12. These episodes were self-terminating, and evaluation had been limited to electrocardiograms (ECGs), which were normal. He had no personal history of syncope or seizures and no family history of arrhythmia, early coronary artery disease (CAD), or sudden death. The patient’s only known cardiac risk factor was cigarette smoking.

ASSESSMENT

On physical examination, the patient was pale, diaphoretic, and tachypneic. His blood pressure was 86/44 mm Hg, and his pulse was >200 bpm. Except for an extremely rapid, regular tachycardia, the cardiovascular examination was unremarkable. The ECG revealed a regular, narrow QRS tachycardia at 250 bpm, diffuse ST depression most marked in the precordial leads, and right axis deviation (Figure 1).

The patient vomited while in the emergency department and continued to complain of left arm discomfort. His symptoms were relieved by intravenous administration of adenosine, which also normalized his sinus rhythm and blood pressure and greatly diminished the ST deviation (Figure 2). The differential diagnosis included atrioventricular nodal reentry tachycardia, atrial flutter with 1:1 atrioventricular conduction, and orthodromic atrioventricular reciprocating tachycardia with a concealed accessory pathway. Because of concern that myocardial ischemia might ensue, the patient was admitted for observation and further evaluation.

DIAGNOSIS

Although initially normal, the patient’s serial cardiac injury markers rose markedly: peak troponin I was 21.76 ng/dL (normal, <0.06), creatine kinase was 1486 mcg/L, and the CK-MB fraction was 203.9 mcg/L (normal, 8 mcg/L). An ECG showed normal ventricular systolic and diastolic function, normal chamber dimensions, and no significant valvular disease. Cardiac catheterization revealed only minimal luminal irregularities of the coronary arteries. Electrophysiology study revealed a concealed left lateral accessory pathway, indicating a diagnosis of orthodromic atrioventricular reciprocating tachycardia. The accessory pathway was successfully ablated.

Data regarding ischemic ECG changes during SVT are limited. In a study of 100 middle-aged SVT patients, 89% had ST segment depression of ≥1.0 mm in at least 1 ECG lead.1 The mean ST depression was 2.2 mm per lead, and the magnitude of depression and number of leads with this abnormality were directly related to heart rate. Greater ST depression occurred with atrioventricular reciprocating tachycardia than with atrioventricular nodal reentry tachycardia, but even marked ST depression (≥4 mm) did not correlate with a history of CAD. In fact, in approximately 50% of the patients, repolarization changes occurred at the onset of atrioventricular nodal reentry tachycardia during electrophysiology study, and the overwhelming majority (93%) of these patients had no CAD.2

Few studies have assessed the significance of ST depression during SVT in relation to the presence of CAD.3,4 However, in a comparison of 39 SVT patients with no prior
diagnosis of CAD, 21 had >1.0 mm ST depression during the arrhythmia, and 18 had no ST changes. There were no significant differences in age, cardiac risk factors, heart rate, or chest pain during SVT episodes in the 2 groups. Cardiac stress tests were normal in all 18 who did not exhibit ST depression during SVT, whereas they were “positive” in 7 of the 21 who did. Coronary angiography confirmed the presence of CAD (≥70% stenosis) in all 7 of these patients. Thus, ST deviation during SVT had positive and negative predictive values of 33 and 100%, respectively, for the presence of CAD.

ST segment depression has been controversially proposed as a potential discriminator between atrioventricular reciprocating tachycardia and atrioventricular nodal reentry tachycardia. It should be noted that this proposal is based on studies that excluded patients with a wide QRS complex during SVT, which would predictably lead to repolarization abnormalities. These findings are also not applicable to patients with atrial fibrillation, who are often older and more likely to have CAD.

Elevation of myocardial injury markers is pivotal in the diagnosis of acute coronary syndromes but might also occur in numerous conditions unassociated with CAD, including myocarditis, pericarditis, heart failure, myocardial toxic drugs, shock, pulmonary embolism, strenuous exercise, and renal insufficiency. Remarkably, elevation of injury markers related to SVT has been described in only a few case reports, and increases in troponin I were generally modest. Although our patient was young and exhibited no evidence of structural heart disease, he had both marked ST depression and injury marker elevation. His episode was prolonged, lasting >90 minutes, and was associated with hypotension, although the predictive value of these factors is not established.

Recent studies indicate that most patients who have ischemic-type ECG changes and positive markers during SVT do not have significant CAD, even in older age groups. A potential mechanism for this phenomenon is an SVT-induced mismatch between myocardial oxygen supply and demand. Reduced diastolic time would decrease the myocardial oxygen supply, and this effect would be compounded by the increased myocardial oxygen demand related to tachycardia, which can result in ischemia/injury and troponin release. In fact, the cardiomyopathy of chronic tachycardia may occur by a similar mechanism. A second potential mechanism, microvascular disease, was not specifically excluded in this patient, but the risk factors for epicardial CAD and for microvascular disease are similar, and current treatment of the latter is largely limited to addressing these underlying risk factors.
Given the prevalence and poor predictive value of ischemic-type ST changes in SVT, over-interpretation of such changes would result in invasive evaluation in many patients without CAD. A more practical diagnostic approach is suggested in Figure 3. After appropriate therapy for arrhythmia, the decision to measure cardiac injury markers should be made based on the clinician’s suspicion of ischemia. It should be noted that there is little data concerning patients with SVT and chest pain but without ischemic ECG changes. Furthermore, elevated troponin, even in association with significant ST depression, must be interpreted in relation to the patient’s pre-test probability of CAD.

**MANAGEMENT**

The benign nature of ST depression in the setting of SVT is well established. The addition of highly sensitive testing of cardiac injury markers to the initial workup of these patients, however, can lead to the false diagnosis of significant epicardial CAD. As our case illustrates, even marked ST depression and considerable elevation of troponin do not necessarily indicate epicardial CAD. Clinical risk stratification followed by stress testing in medium- and high-risk patients is a prudent approach to this not uncommon clinical problem.

After the successful ablation of the concealed left lateral accessory pathway and quitting smoking, our patient had no further palpitations or arm heaviness over the next 11 months.

**References**

The skin is the largest organ in the human body, both in terms of surface area and mass, and it performs a multitude of protective, regulatory, and sensory functions. However, it also is subject to a multitude of primary and secondary disorders, many of which have poorly understood etiologies. We describe one such case here.

PRESENTATION
A 25-year-old African American female came to our clinic with a 1-month history of pruritus and tenderness of her posterior neck, which she attributed to a “cyst” in that location. She denied systemic symptoms. Her past medical history was significant for insulin-dependent diabetes mellitus and a soft-tissue infection of the leg 1 year prior to presentation, and she was on insulin, lisinopril, and lovastatin. Her family history included insulin-dependent diabetes mellitus and eczema.

ASSESSMENT
Physical examination revealed a firm, nonpitting, hyperpigmented plaque with indistinct borders on her posterior neck beginning at her hairline and extending down the neck and upper back (Figure 1). The remainder of her back was supple, as were the upper extremities. Biopsy of the involved area revealed a thickened dermis with separation of collagen bundles. Staining with alcian blue (Figure 2) revealed extensive interstitial mucin deposition throughout the reticular dermis.

Her serum glucose was 148 mg/dL, and her total serum protein was 8.5 g/dL (normal 6.0-8.3). Serum protein electrophoresis revealed no monoclonal gammopathy. A chronic inflammatory response was suggested by an increase in polyclonal IgG levels (1.8 g/dL; normal 0.6-1.6). The patient also had elevated urine protein, and electrophoresis revealed a pattern of mixed glomerular and tubular proteinuria consistent with diabetic renal disease.

DIAGNOSIS
The extensive interstitial mucin deposition in the patient’s skin indicated that her symptoms were caused by one of the cutaneous mucinoses, a group of connective-tissue disorders characterized by the accumulation of mucin in the skin. The members of this large, heterogeneous group of disorders have a number of different morphologic presentations and are easily misdiagnosed.

In the present case, the diffuse, woodlike thickening of the dermis indicated scleredema, an uncommon and ill-understood condition. Histologically, scleredema appears as unaltered epidermis with large, widely spaced, collagen bundles. With use of special stains or electron microscopy, the spaces can be properly visualized as mucin deposits. In the vast majority of cases, the pathology of this uncommon disorder remains limited to the skin, although visceral involvement, including cardiomyopathy, has been described where mucin can be seen in the cardiac muscle.1-2 A variety of clinical situations are associated with scleredema, but most fall within 1 of 3 subtypes. Each subtype has its own constellation of associated factors and course of illness.

The most frequently encountered scleredema subtype, which occurs in non-diabetic young adults, is an acute condition that may follow a febrile illness (usually streptococcal).3 The skin of the cervical and facial area quickly becomes hardened and taut, which can result in difficulty opening the mouth and swallowing. This form of the disease has a rapid onset and tends to resolve quickly (within months of onset).3 The second scleredema subtype resembles the first subtype in its symptoms but has a more gradual onset. These patients have persistent disease and associated monoclonal gammopathy (most commonly IgG) or multiple myeloma. The gammopathy is commonly undetectable when symptoms first arise; in fact, it can be clinically silent for over a decade after cutaneous presentation, thus requiring periodic monitoring.4

Requests for reprints should be addressed to Julie T. Templet, MD, Drexel University College of Medicine, Department of Dermatology, 219 N. Broad Street, 4th Floor, Philadelphia, PA 19107.
E-mail address: julietemplet@yahoo.com

0002-9343/$ -see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjmed.2007.06.019
The remaining scleredema subtype, known as scleredema diabeticorum, occurs in a distinct milieu. The archetypal patient afflicted by this form of scleredema is the obese male over 40 years of age with uncontrolled insulin-dependent diabetes. The posterior neck and back harden, and overlying erythema is sometimes present. The cutaneous changes in scleredema diabeticorum are recalcitrant to treatment, and the course of the disease is unaffected by glycemic management. In the present case, our patient’s condition was best categorized as scleredema diabeticorum, although her youth was atypical for this subtype.

Other cases of scleredema that are not readily classified into 1 of the 3 subtype categories also have been documented. Some associations with underlying malignancy, including adenocarcinoma of the gallbladder and insulina, have been reported. Recently, a case of scleredema was reported in a patient undergoing infliximab therapy. When the patient was taken off infliximab, the symptoms resolved, only to return when infliximab therapy was reinitiated.

The differential diagnosis for scleredema includes scleroderma, cellulitis, scleromyxedema, and other cutaneous mucinoses. Scleroderma also causes hardened skin, but unlike scleredema, it can afflict the extremities and is associated with Raynaud’s phenomenon, telangiectases, and antinuclear antibodies. Because scleredema associated with diabetes results in erythema, patients may be misdiagnosed with cellulitis. Scleromyxedema, a generalized primary cutaneous mucinosis that also has associated monoclonal gammopathy, can be differentiated from scleredema by the diffuse symmetric eruption of waxy papules. Other cutaneous mucinoses, including reticular erythematous, dysthyroidotic, and follicular mucinoses, can usually be distinguished from scleredema on a clinical basis.

The precipitant for the aberrant tissue structure of scleredema remains unknown. Proposed theories include sensitization to collagen by an infectious agent, autoimmunity, and non-enzymatic glycosylation of collagen rendering it resistant to collagenase activity. Alternatively, Koga has suggested that microvascular damage and hypoxia stimulate mucin and collagen synthesis. Regardless of the etiology.


ECG IMAGE OF THE MONTH
Julia H. Indik, MD, PhD, Section Editor

A Heart Aflutter
Ahmad Khraisat, Sarabjeet Singh, Rohit Arora, Eshraq Al-Jaghbeer
Section of Cardiology, Department of Medicine, The Chicago Medical School.

PRESENTATION
Most ventricular tachycardias encountered in clinical practice occur in patients who have structural heart disease. In the present case, a 27-year-old female attorney presented with palpitations of 1-day duration accompanied by dizziness, shortness of breath, and chest tightness. She had experienced similar, but briefer, episodes in the previous few months, without fainting. Her past medical history was unremarkable, and she was not on any medications.

ASSESSMENT
Lying supine in bed, the patient appeared anxious and had a blood pressure of 115/67 mm Hg and a pulse of 89 bpm. The physical examination and laboratory workup were otherwise unremarkable.

An initial electrocardiogram (ECG) showed a wide-QRS-complex tachycardia at a rate of 183 bpm with a QRS width of approximately 140 msec (Figure 1). The baseline ECG was otherwise normal (Figure 2). An echocardiogram with attention to the right ventricle was within normal limits, and an exercise stress test provoked the same monomorphic tachycardia observed previously.

DIAGNOSIS
The patient’s monomorphic ventricular tachycardia was characterized by negative QRS complexes in V1 and V2, indicating a left bundle-branch block morphology with inferior axis (positive complexes in the inferior leads: II, III and AVF), and an otherwise normal baseline ECG and echocardiogram. These characteristics, the paroxysmal nature of the tachycardia, and its occurrence in a young female were suggestive of a right ventricular outflow tract tachycardia. In North America, 70% of cases of idiopathic ventricular tachycardia arise from the right ventricle, chiefly at the right ventricular outflow tract just inferior to the pulmonic valve. Two phenotypic forms of right ventricular outflow tract tachycardia are known to occur, both of which occurred in our patient. These forms are nonsustained, repetitive, monomorphic ventricular tachycardia (Figure 3) and paroxysmal, exercise-induced, sustained ventricular tachycardia (Figure 1). Both phenotypes are terminated by the administration of adenosine.

Symptoms of right ventricular outflow tract tachycardia typically arise in the third to fifth decade of life and are usually precipitated by exercise or emotional stress. Most patients present with palpitations (80%) or presyncope (50%), which are more common than frank syncope. Baseline ECGs recorded during sinus rhythm in patients with right ventricular outflow tract tachycardia can help distinguish it from the more serious condition of arrhythmogenic right ventricular cardiomyopathy/dysplasia. The ECG is more often abnormal in the latter condition, most commonly showing persistently inverted T waves in the right precordial leads (V1, V2, and V3).

In arrhythmogenic right ventricular cardiomyopathy/dysplasia, echocardiography typically shows right ventricular dilatation with regional wall motion abnormalities. Cardiac magnetic resonance imaging (MRI) performed in specialized centers can detect fatty replacement of the right ventricular myocardium, but this parameter is the least reliable and reproducible. Wall motion abnormalities, right ventricular enlargement, and ectasia of the right ventricular outflow tract are more reliable and reproducible MRI parameters. Wall motion abnormalities can also be found by right ventricular angiography, which may also reveal aneurysms as areas of increased volume with transversely arranged hypertrophic trabeculae in the apical region distal to the moderator band.

Right ventricular outflow tract tachycardia has been historically regarded as idiopathic, but this perception is a consequence of reliance on conventional imaging and diagnostic techniques, such as stress testing, echocardiography, and coronary angiography. These tests usually yield normal results. On the other hand, MRI may show minor abnormalities of the right ventricle in up to 70% of patients,
Figure 1  Twelve-lead ECG showing sustained right ventricular outflow tract tachycardia with left bundle-branch block morphology (negative QRS in V1 and V2) and inferior axis (positive QRS in II, III, and AVF).

Figure 2  Baseline 12-lead ECG showing normal sinus rhythm.

Figure 3  ECG showing repetitive monomorphic right ventricular outflow tract tachycardia and premature ventricular contractions.
including focal thinning (fatty replacement), diminished systolic wall thickening, and abnormal wall motion. A summary of the clinical and electrophysiological differences between arrhythmogenic right ventricular cardiomyopathy/dysplasia and right ventricular outflow tract tachycardia is detailed in Table 1.

Clinical evidence has implicated several electrophysiological mechanisms in right ventricular outflow tract tachycardia, including abnormal automaticity and triggered activity. The most common form of right ventricular outflow tract tachycardia is related to triggered activity arising from delayed afterdepolarization, and is thought to depend on intracellular calcium overload and cyclic adenosine monophosphate. Such a ventricular tachycardia is therefore frequently adenosine sensitive, may terminate with vagal maneuvers, and is facilitated by catecholamines.

### MANAGEMENT

Long-term treatment options for right ventricular outflow tract tachycardia include medical therapy and radiofrequency ablation. In view of the fact that right ventricular outflow tract tachycardia is a benign tachyarrhythmia unrelated to ischemic heart disease or cardiomyopathy, an implantable cardioverter defibrillator is not indicated. Because structural heart disease is absent, beta-blockers or calcium channel blockers can be used. Radiofrequency ablation has a cure rate of 90%, making it the preferred treatment, given the relative youth of patients with this arrhythmia. Our patient was initially treated with beta-blockers. After treatment options were discussed, she was taken to the electrophysiology laboratory, where mapping confirmed a right ventricular outflow origin that was subsequently ablated successfully. The patient tolerated the procedure well and was discharged with an event recorder.

### References

No Simple Sore Throat

William J. Salyers, Jr., MD,a Christina Schnose, BA,a Adam Zarchan, MDb

aDepartments of Internal Medicine and bDiagnostic Radiology, University of Kansas School of Medicine—Wichita.

PRESENTATION

The case of a previously healthy 24-year-old woman with a chief complaint of sore throat provided an opportunity to diagnose and treat an unusual entity. Despite outpatient treatment with clarithromycin, the patient’s odynophagia worsened, and she developed a fever. She was hospitalized, treated with ceftriaxone, and subsequently discharged home on levofloxacin and prednisone. Her sore throat improved over the next week, but approximately 2 weeks after the initial onset of her illness, she was readmitted for right-sided swelling of the neck, severe pain, and dysphagia.

The patient’s past medical history was significant only for nephrolithiasis. She had no children and no prior history of miscarriages. She was on no chronic medications and took only ibuprofen as needed for pain. Additionally, she denied tobacco use. Her mother and grandmother each had a history of deep vein thrombosis and pulmonary embolism.

ASSESSMENT

The patient had a fever of 100.4°F (38.0°C), and she was hypotensive, with a blood pressure of 90/62 mm Hg. An examination of her neck revealed an asymmetric mass and right-sided swelling with induration, which altogether measured approximately 6 x 6 cm. The angle of her right mandible was tender to palpation, and right-sided anterior cervical lymphadenopathy was present. She was noted to have trismus. Her lungs were clear to auscultation bilaterally, and examination of her upper and lower extremities revealed no erythema, swelling, or pain. Laboratory tests disclosed leukocytosis (white blood cell count, 22.6 x 10^3 cells/mm^3) with 9% bands and an elevated erythrocyte sedimentation rate of 45 mm/hr.

DIAGNOSIS

Computed tomography of the neck, with and without contrast, indicated an abscess adjacent to the right sternocleidomastoid muscle and another fluid collection alongside the right medial pterygoid muscle (Figure 1). Thrombosis of the right internal jugular vein bordered both pockets. A cavitary lesion in the right upper lobe of the lung and a peripheral nodule in the left upper lobe also were disclosed. Contrast-enhanced computed tomography of the chest showed cavitary lesions, as well as peripheral nodules in the lungs bilaterally, findings consistent with septic pulmonary emboli (Figure 2).

The patient was diagnosed with Lemierre syndrome. Also known as postanginal sepsis or necrobacillosis, Lemierre syndrome occurs secondary to an oropharyngeal infection and is characterized by thrombophlebitis of the internal jugular vein with resulting metastatic lesions. Our patient’s oropharyngeal infection was followed by suppurative jugular venous thrombosis and development of septic pulmonary emboli. Because her family history was significant for deep vein thrombosis and pulmonary embolism, a hypercoagulable workup was performed. She was found to have a low-medium positive anticardiolipin IgM titer at 64 MPL U/mL (normal, 0-9 MPL U/mL).

Fusobacterium necrophorum is the most common pathogen, causing up to 81% of cases. Other bacteria isolated from either blood or abscess cultures include Bacteroides species, Streptococcus viridans, Peptostreptococcus species, Group B and group C Streptococcus species, Streptococcus pyogenes, Staphylococcus epidermidis, non-multidrug-resistant methicillin-resistant Staphylococcus aureus, and Enterococcus species. While metastatic lesions can cause septic arthritis and rarely, osteomyelitis, liver abscesses, and soft tissue infections, the lung is the most common site of septic emboli with involvement in 80-97% of cases.

Radiologic evaluation is a critical piece in solving the puzzle of Lemierre syndrome. The important findings can
be demonstrated by ultrasound, computed tomography, and magnetic resonance imaging. Each modality has benefits and drawbacks. Ultrasound reliably visualizes jugular venous thrombosis by demonstrating a noncompressible thrombus and loss of color flow. It does not use ionizing radiation, and it is inexpensive and convenient.\textsuperscript{6} Although ultrasound cannot visualize the jugular vein behind the clavicle or at the skull base, these limitations are rarely clinically relevant, as the extent of thrombosis does not typically affect clinical management.\textsuperscript{7}

Computed tomography can evaluate the soft tissues surrounding the jugular vein more fully and visualize the septic pulmonary emboli characteristic of Lemierre syndrome. False negative results for jugular venous thrombosis can occur as a result of vascular flow phenomena and the variable appearance of the clot over time. However, the related loss of both surrounding soft tissue planes and peripheral enhancement might still suggest the finding.\textsuperscript{8} Magnetic resonance imaging might be more sensitive for detection of jugular venous thrombosis due to loss of the normal flow void, but it is expensive and time-consuming, making it less than ideal for patients who are critically ill.\textsuperscript{6} As a result, computed tomography is the current imaging modality of choice for patients with suspected Lemierre syndrome.

**MANAGEMENT**

The mainstays of treatment for Lemierre syndrome include extended antibiotic therapy with initial coverage for anaerobic organisms and surgical drainage if an abscess is present. Use of anticoagulation is controversial; no studies evaluate the efficacy of antibiotics alone or in conjunction with anticoagulation therapy.\textsuperscript{9} Some anecdotal evidence showed anticoagulation in combination with antibiotics will resolve symptoms more rapidly and prevent further metastases.\textsuperscript{10}

Our patient underwent early surgical incision and drainage of the abscesses and was treated with intravenous ceftriaxone and clindamycin. Although blood cultures were negative, cultures from the fluid collection grew *Porphyromonas asaccharolytica* and group C *Streptococcus* species. *Porphyromonas* species are gram-negative anaerobic pathogens found in oropharyngeal flora. These organisms have been found in deep facial infections, but they have rarely been reported in connection with Lemierre syndrome.\textsuperscript{11} A recent MEDLINE search (keywords: Lemierre syndrome; postanginal sepsis; necrobacillosis AND *Porphyromonas*) revealed only 3 reports of a correlation between Lemierre syndrome and *Porphyromonas* species.\textsuperscript{12-14} Although *Fusobacterium* species were not present, previous antibiotic use prior to her presentation might have suppressed the bacteria. Ramirez et al found that patients with Lemierre syndrome who had previously received antibiotics did not grow *Fusobacterium necrophorum* from blood cultures, including those who had positive blood cultures before initiation of antibiotic therapy.\textsuperscript{9}

Because our patient had a positive anticardiolipin antibody titer, we prescribed enoxaparin and warfarin therapy with a goal international normalized ratio of 2.0-3.0. She responded well to treatment over the following week and was dismissed to follow-up with instructions to continue taking amoxicillin and clavulanate along with anticoagulants.

**References**


CLINICAL RESEARCH STUDY

Obesity Paradox in Patients with Hypertension and Coronary Artery Disease

Seth Uretsky, MD, Franz H. Messerli, MD, Sripal Bangalore, MD, MHA, Annette Champion, MBA, Rhonda M. Cooper-DeHoff, PharmD, Qian Zhou, PhD, Carl J. Pepine, MD

ABSTRACT

PURPOSE: An obesity paradox, a “paradoxical” decrease in morbidity and mortality with increasing body mass index (BMI), has been shown in patients with heart failure and those undergoing percutaneous coronary intervention. However, whether this phenomenon exists in patients with hypertension and coronary artery disease is not known.

METHODS: A total of 22,576 hypertensive patients with coronary artery disease (follow-up 61,835 patient years, mean age 66 ± 9.8 years) were randomized to a verapamil-SR or atenolol strategy. Dose titration and additional drugs (trandolapril and/or hydrochlorothiazide) were added to achieve target blood pressure control according to the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure targets. Patients were classified into 5 groups according to baseline BMI: less than 20 kg/m² (thin), 20 to 25 kg/m² (normal weight), 25 to 30 kg/m² (overweight), 30 to 35 kg/m² (class I obesity), and 35 kg/m² or more (class II-III obesity). The primary outcome was first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS: With patients of normal weight (BMI 20 to <25 kg/m²) as the reference group, the risk of primary outcome was lower in the overweight patients (adjusted hazard ratio [HR] 0.77, 95% confidence interval [CI], 0.70-0.86, \(P < .001\)), class I obese patients (adjusted HR 0.68, 95% CI, 0.59-0.78, \(P < .001\)), and class II to III obese patients (adjusted HR 0.76, 95% CI, 0.65-0.88, \(P < .001\)). Class I obese patients had the lowest rate of primary outcome and death despite having smaller blood pressure reduction compared with patients of normal weight at 24 months (−17.5 ± 21.9 mm Hg/−9.8 ± 12.4 mm Hg vs −20.7 ± 23.1 mm Hg/−10.6 ± 12.5 mm Hg, \(P < .001\)).

CONCLUSION: In a population with hypertension and coronary artery disease, overweight and obese patients had a decreased risk of primary outcome compared with patients of normal weight, which was driven primarily by a decreased risk of all-cause mortality. Our results further suggest a protective effect of obesity in patients with known cardiovascular disease in concordance with data in patients with heart failure and those undergoing percutaneous coronary intervention. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Beta-blockers; Calcium antagonists; Coronary artery disease; Hypertension; INVEST; Obesity paradox

Obesity has been an established risk factor for increased cardiovascular mortality in men and women.\(^1\)\(^-\)\(^10\) The increased risk of obesity for cardiovascular disease is thought to be mediated in part by the clustering of risk factors such as hypertension, hypercholesterolemia, and diabetes mellitus (metabolic syndrome).\(^11\) In an epidemiologic study of 527,265 men and women, there was an increased risk of death associated with excess body weight during midlife.\(^7\) Similarly, in a Korean cohort of 1,213,829 men and women, obese people had higher rates of death than people of normal weight.\(^8\)
Although obesity increases the likelihood of metabolic syndrome and its consequences, obesity has not been associated with a worse outcome in all patient populations. In patients with known cardiovascular disease (eg, those with heart failure), those undergoing percutaneous coronary interventions, and those with known coronary artery disease referred for single-photon emission computed tomography, an “obesity paradox,” a paradoxical decrease in morbidity and mortality with increasing body mass index (BMI), has been described.\(^\text{12-18}\) In patients undergoing percutaneous coronary intervention, obese patients had a 5.7% absolute decrease in incidence of death at 1 year compared with normal-weight patients.\(^\text{14}\) In patients with congestive heart failure there was a 19% relative reduction in the risk of death in obese patients compared with normal-weight patients.\(^\text{12}\) These findings, in contrast with earlier literature, suggest a protective effect associated with obesity in patients with known cardiovascular disease.

However, in patients with hypertension and coronary artery disease, the role of BMI in the risk of cardiovascular events is not defined. The objective of the present study was to investigate the effect of obesity on cardiovascular outcomes in treated hypertensive patients with known coronary artery disease. To study this relationship, the INternational VErapamil SR-trandolopril STudy (INVEST) cohort provided an ideal population.\(^\text{19}\)

### METHODS

**Study Design**

INVEST was a prospective, randomized, international study of 22,572 patients with hypertension and coronary artery disease. The inclusion and exclusion criteria, study design, and results have been published elsewhere.\(^\text{19}\) In brief, eligible patients were randomized to a verapamil-SR–based or an atenolol-based treatment strategy to achieve the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure targets (\(<140/90\) mm Hg or \(<130/85\) mm Hg in those with diabetes or renal dysfunction).\(^\text{20}\) Patients were eligible if they were 50 years or older and had essential hypertension and documented coronary artery disease. Coronary artery disease was defined as a myocardial infarction 3 months or more before enrollment, coronary angiogram with more than 50% stenosis in at least 1 major coronary artery, angina pectoris, or evidence of ischemia on at least 2 different modalities of stress tests (electrocardiogram, echocardiogram, radionuclide scan) that were consistent. Exclusion criteria included patients receiving beta-blockers within 2 weeks of randomization.

This analysis was designed to study the effects of obesity in patients with hypertension and coronary artery disease. At each study visit, an extensive cardiovascular examination was performed, and body weight and height were recorded into the electronic web-based data capture system. BMI was calculated by the system as weight in kilograms/height in meters squared, stored in the database, and recorded in the patient’s visit summary, which was printed for the patient’s medical record.

### Statistical Analysis

Patients were classified into 5 groups according to their baseline BMI: less than 20 kg/m\(^2\) (thin), 20 to 25 kg/m\(^2\) (normal weight), 25 to 30 kg/m\(^2\) (overweight), 30 to 35 kg/m\(^2\) (class I obesity), and 35 kg/m\(^2\) or more (class II-III obesity). Four patients with presumed erroneous data, defined as BMI greater than 100 kg/m\(^2\), were excluded. All analyses were conducted on the remaining 22,572 patients in the intention-to-treat population. Primary outcome was the first occurrence of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes were all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke with cardiovascular-related death as an additional outcome. Patient groups were compared using analysis of variance for continuous variables and the chi-square test for categoric variables. For each outcome, a single unadjusted Cox proportional hazards model was used to compare risk among the 5 BMI categories (BMI 20-25 kg/m\(^2\) as reference). A stepwise Cox proportional hazard regression model was used to evaluate the role of BMI on the risk of primary outcome. Prespecified covariates forced into the model included treatment, age, race (white as reference), gender, history of myocardial infarction, and heart failure. Other baseline covariates were selected for the model on the basis of a \(P\) value of .10 or less. All analyses were performed using standard software (SAS 9.1.3, SAS Institute Inc, Cary, NC).

### RESULTS

**Baseline Characteristics**

The mean age was 66 ± 9.8 years, and the mean follow-up was 2.7 years (range, 1 day to 5.4 years) with 61,835 patient years accumulated. Of the 22,572 patients included in this analysis, 2.2% were thin, 20.0% were normal weight, 39.9%...
were overweight, 24.6% had class I obesity, and 13.2% had class II to III obesity. Pertinent baseline characteristics by BMI class are summarized in Table 1. Compared with class II to III obesity, normal-weight patients, overweight and class I to III obese patients were younger, had a history of diabetes and hypercholesterolemia, and were less likely to be a current smoker or to have a history of cancer, previous myocardial infarction, stroke/transient ischemic attack (TIA), or peripheral vascular disease.

**Blood Pressure Control**

Class I obese patients had a lower baseline mean systolic blood pressure and higher baseline mean diastolic blood pressure when compared with normal-weight patients (Table 2). At 24 months of treatment, class I obese patients had a lower reduction in both systolic blood pressure and diastolic blood pressure when compared with normal-weight patients (–17.5 ± 21.9 mm Hg/–9.8 ± 12.4 mm Hg vs –20.7 ± 23.1 mm Hg/–10.6 ± 12.5 mm Hg, P < .001), and

---

**Table 1** Baseline Characteristics of Patients According to Baseline Body Mass Index Category

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Thin (n = 505)</th>
<th>Normal Weight (n = 4256)</th>
<th>Overweight (n = 9012)</th>
<th>Class I Obesity (n = 5560)</th>
<th>Class II-III Obesity (n = 2969)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>18.5 ± 1.2</td>
<td>23.1 ± 1.3</td>
<td>27.5 ± 1.4</td>
<td>32.1 ± 1.4</td>
<td>39.5 ± 4.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>72.0 ± 10.3</td>
<td>69.3 ± 10.3</td>
<td>66.4 ± 9.6</td>
<td>64.4 ± 9.0</td>
<td>62.3 ± 8.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age ≥70 y (%)</td>
<td>54.7</td>
<td>46.9</td>
<td>34.6</td>
<td>26.3</td>
<td>18.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>71.1</td>
<td>52.3</td>
<td>47.5</td>
<td>51.6</td>
<td>63.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes (%)†</td>
<td>12.7</td>
<td>20.3</td>
<td>26.6</td>
<td>33.1</td>
<td>39.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>36.2</td>
<td>51.2</td>
<td>56.0</td>
<td>57.9</td>
<td>56.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Renal insufficiency (%)</td>
<td>2.4</td>
<td>2.0</td>
<td>1.9</td>
<td>1.5</td>
<td>2.3</td>
<td>.075</td>
</tr>
<tr>
<td>Heart failure class I-III (%)</td>
<td>9.5</td>
<td>5.8</td>
<td>4.7</td>
<td>5.2</td>
<td>7.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>26.7</td>
<td>15.4</td>
<td>11.7</td>
<td>11.1</td>
<td>10.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cancer (%)</td>
<td>4.0</td>
<td>4.3</td>
<td>3.4</td>
<td>2.9</td>
<td>2.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>35.6</td>
<td>34.8</td>
<td>32.4</td>
<td>30.6</td>
<td>28.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>14.7</td>
<td>16.0</td>
<td>16.4</td>
<td>15.8</td>
<td>13.7</td>
<td>.012</td>
</tr>
<tr>
<td>Percutaneous coronary intervention (%)</td>
<td>12.7</td>
<td>13.7</td>
<td>15.4</td>
<td>16.0</td>
<td>14.1</td>
<td>.003</td>
</tr>
<tr>
<td>Stroke/TIA (%)</td>
<td>9.7</td>
<td>9.1</td>
<td>6.9</td>
<td>6.6</td>
<td>6.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LVH (%)</td>
<td>22.2</td>
<td>22.5</td>
<td>21.7</td>
<td>21.6</td>
<td>22.4</td>
<td>.711</td>
</tr>
<tr>
<td>Angina pectoris (%)</td>
<td>66.3</td>
<td>65.8</td>
<td>65.8</td>
<td>67.0</td>
<td>69.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>14.9</td>
<td>12.8</td>
<td>11.5</td>
<td>11.5</td>
<td>12.4</td>
<td>.030</td>
</tr>
<tr>
<td>Aspirin/antiplatelet therapy (%)</td>
<td>48.5</td>
<td>58.1</td>
<td>58.1</td>
<td>56.3</td>
<td>52.1</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

BMI = body mass index; CAGB = coronary artery bypass graft; LVH = left ventricular hypertrophy; MI = myocardial ischemia; TIA = transient ischemic attack.

Values expressed as mean ± standard deviation unless otherwise indicated.

*Chi-square test for categoric variables and 1-way analysis of variance for numeric variables.

†History of or currently taking antidiabetic or lipid-lowering medications.

---

**Table 2** Blood Pressure at Baseline and 24 Months by Baseline Body Mass Index Category

<table>
<thead>
<tr>
<th></th>
<th>Thin (n = 301)</th>
<th>Normal Weight (n = 3094)</th>
<th>Overweight (n = 6358)</th>
<th>Class I Obesity (n = 3950)</th>
<th>Class II-III Obesity (n = 1986)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure at baseline (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>154.4 ± 21.9</td>
<td>151.8 ± 19.8</td>
<td>151.0 ± 19.0</td>
<td>149.9 ± 18.7</td>
<td>150.3 ± 19.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85.6 ± 11.5</td>
<td>86.8 ± 12.4</td>
<td>87.6 ± 11.7</td>
<td>87.7 ± 11.5</td>
<td>88.1 ± 11.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean change in blood pressure at 24 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>−22.9 ± 25.0</td>
<td>−20.7 ± 23.1</td>
<td>−19.6 ± 22.3</td>
<td>−17.5 ± 21.9</td>
<td>−15.8 ± 21.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>−9.8 ± 12.2</td>
<td>−10.6 ± 12.5</td>
<td>−10.4 ± 12.3</td>
<td>−9.8 ± 12.4</td>
<td>−9.2 ± 12.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood pressure control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(140/90 mm Hg), %</td>
<td>69.1</td>
<td>73.2</td>
<td>73.3</td>
<td>70.4</td>
<td>63.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>JNC VI blood pressure control, %</td>
<td>65.4</td>
<td>67.3</td>
<td>65.6</td>
<td>59.8</td>
<td>51.5</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

BMI = body mass index; JNC = Joint National Committee.

*Results from a chi-square test for blood pressure control, 1-way analysis of variance for baseline blood pressure, and analysis of covariance for blood pressure changes with BMI category as the factor and baseline blood pressure as covariate.
a lower percentage of class I obese patients reached the target blood pressure goal of 140/90 mm Hg and the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure target when compared with normal-weight patients.

Medication Use

The mean use of study and nonstudy antihypertensive drugs was higher in the higher BMI groups for both the calcium channel blocker strategy and atenolol-based strategy (mean number of study and nonstudy antihypertensive drugs during 24 months: thin = 2.3/2.3, normal weight = 2.4/2.4, overweight = 2.5/2.6, class I obesity = 2.7/2.7, class II-III obesity = 3.0/3.0). The percentage of patients requiring 3 or more antihypertensive drugs was higher in the higher BMI categories but did not differ between treatment strategies in a given BMI cohort at 24 months (Figure 1). Most patients required 3 or more antihypertensive drugs at 24 months.

Primary and Secondary Outcomes

The relationship between the incidence of the primary outcome and BMI followed a J-shaped curve with the lowest incidence in the class I obese group. The incidence of the primary outcome was lower in overweight, class I, and class II to III obese patients compared with normal-weight patients despite better blood pressure control in the normal-weight patients at 24 months (Table 3 and Figure 2). The secondary outcome of all-cause mortality and cardiovascular-related death was lower in overweight, class I, and class II to III obese patients compared with normal-weight patients. For the secondary outcomes of nonfatal myocardial infarction and nonfatal stroke there was no difference comparing overweight, class I, and class II to III obese patients with normal-weight patients.

In a multivariate analysis, higher BMI, Asian or Hispanic race (vs white), and hypercholesterolemia were associated with a decreased risk for the primary outcome (Table 4). The following were associated with an increased risk of

<table>
<thead>
<tr>
<th>Event</th>
<th>BMI Category</th>
<th>Subjects with Events (%)</th>
<th>Total Subjects</th>
<th>HR*</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>Thin</td>
<td>113 (22.4%)</td>
<td>505</td>
<td>1.74</td>
<td>1.42-2.13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Normal weight (reference)</td>
<td>593 (13.1%)</td>
<td>4526</td>
<td>0.71</td>
<td>0.64-0.78</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>858 (9.5%)</td>
<td>9012</td>
<td>0.57</td>
<td>0.51-0.65</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Class I obesity</td>
<td>445 (8.0%)</td>
<td>5560</td>
<td>0.61</td>
<td>0.53-0.71</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Class II-III obesity</td>
<td>260 (8.8%)</td>
<td>2969</td>
<td>0.65</td>
<td>0.59-0.74</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death</td>
<td>Thin</td>
<td>98 (19.4%)</td>
<td>505</td>
<td>1.85</td>
<td>1.49-2.30</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Normal weight (reference)</td>
<td>484 (10.7%)</td>
<td>4526</td>
<td>0.66</td>
<td>0.59-0.74</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>656 (7.3%)</td>
<td>9012</td>
<td>0.52</td>
<td>0.45-0.59</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Class I obesity</td>
<td>329 (5.9%)</td>
<td>5560</td>
<td>0.57</td>
<td>0.49-0.68</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Class II-III obesity</td>
<td>199 (6.7%)</td>
<td>2969</td>
<td>0.55</td>
<td>0.49-0.68</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiovascular-related death</td>
<td>Thin</td>
<td>40 (7.9%)</td>
<td>505</td>
<td>1.56</td>
<td>1.12-2.19</td>
<td>.009</td>
</tr>
<tr>
<td></td>
<td>Normal weight (reference)</td>
<td>233 (5.1%)</td>
<td>4526</td>
<td>0.70</td>
<td>0.59-0.82</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>332 (3.7%)</td>
<td>9012</td>
<td>0.57</td>
<td>0.42-0.63</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Class I obesity</td>
<td>157 (2.8%)</td>
<td>5560</td>
<td>0.55</td>
<td>0.48-0.76</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Class II-III obesity</td>
<td>100 (3.4)</td>
<td>2969</td>
<td>0.60</td>
<td>0.48-0.76</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>Thin</td>
<td>7 (1.4%)</td>
<td>505</td>
<td>1.22</td>
<td>0.51-2.46</td>
<td>.78</td>
</tr>
<tr>
<td></td>
<td>Normal weight (reference)</td>
<td>57 (1.3%)</td>
<td>4526</td>
<td>1.07</td>
<td>0.78-1.46</td>
<td>.69</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>124 (1.4%)</td>
<td>9012</td>
<td>1.02</td>
<td>0.73-1.44</td>
<td>.89</td>
</tr>
<tr>
<td></td>
<td>Class I obesity</td>
<td>76 (1.4%)</td>
<td>5560</td>
<td>1.02</td>
<td>0.73-1.44</td>
<td>.89</td>
</tr>
<tr>
<td></td>
<td>Class II-III obesity</td>
<td>40 (1.3%)</td>
<td>2969</td>
<td>0.99</td>
<td>0.66-1.48</td>
<td>.96</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>Thin</td>
<td>13 (2.6%)</td>
<td>505</td>
<td>1.83</td>
<td>1.01-3.32</td>
<td>.047</td>
</tr>
<tr>
<td></td>
<td>Normal weight (reference)</td>
<td>65 (1.4%)</td>
<td>4526</td>
<td>0.80</td>
<td>0.59-1.09</td>
<td>.15</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>106 (1.2%)</td>
<td>9012</td>
<td>0.77</td>
<td>0.55-1.09</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td>Class I obesity</td>
<td>65 (1.2%)</td>
<td>5560</td>
<td>0.65</td>
<td>0.42-1.01</td>
<td>.054</td>
</tr>
</tbody>
</table>

BMI = body mass index; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction.
*Unadjusted HRs.
reaching primary outcome: increasing age, thin body, male gender, history of myocardial infarction, congestive heart failure, US resident, coronary artery bypass graft or angioplasty, peripheral vascular disease, renal insufficiency, smoking (ever), previous stroke or TIA, and diabetes.

By using normal-weight patients as the reference group, the risk of primary outcome was lower in the overweight (adjusted hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.70-0.86, \( P < .001 \)), class I (adjusted HR 0.68, 95% CI, 0.59-0.78, \( P < .001 \)), and class II to III obese patients (adjusted HR 0.76, 95% CI, 0.65-0.88, \( P < .001 \)), and higher in thin patients (adjusted HR 1.52, 95% CI, 1.24-1.86, \( P < .001 \)).

In each BMI category, men had a higher rate of primary outcome than women (Figure 3). In a subgroup analysis of patients with a history of congestive heart failure and percutaneous coronary intervention, class I obese patients had a 6.6% and 7.5% lower incidence of the primary outcome, respectively, than normal-weight patients. However, the incidence of primary outcome in class II to III obese patients was higher than in class I obese patients, including the subgroups with heart failure and previous percutaneous coronary intervention.

### Primary Outcome and Age

In general, for each BMI category there was an increased incidence of the primary outcome with age for men and women (Figures 4 and 5). For a given age and gender, the relationship between BMI and primary outcome followed a J-shaped curve with the lowest incidence of primary outcome in overweight and class I obese patients, although sample sizes for some of the age groups were small.

### DISCUSSION

This study addressed the effect of BMI on cardiovascular outcomes in a cohort of patients with hypertension and coronary artery disease. Our study is in agreement with previous studies that observed an obesity paradox in patients with previous cardiovascular disease.

### Body Mass Index and Cardiovascular Risk

Epidemiologic studies have described obesity as an independent risk factor for cardiovascular disease and death.\(^\text{1-3,16}\) In a recent analysis of the Framingham cohort, overweight subjects were found to have increased risk for developing cardiovascular disease compared with normal-

---

**Table 4** Stepwise Model Risk for Primary Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin (vs normal)</td>
<td>1.52</td>
<td>1.24-1.86</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Overweight (vs normal)</td>
<td>0.77</td>
<td>0.70-0.86</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Class I obesity (vs normal)</td>
<td>0.68</td>
<td>0.59-0.77</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Class II-III obesity (vs normal)</td>
<td>0.76</td>
<td>0.65-0.88</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (10-y increments)</td>
<td>1.63</td>
<td>1.56-1.71</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Strategy</td>
<td>0.97</td>
<td>0.89-1.05</td>
<td>.44</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>1.12</td>
<td>1.02-1.23</td>
<td>.013</td>
</tr>
<tr>
<td>Race (vs white)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.11</td>
<td>0.98-1.26</td>
<td>.09</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.90</td>
<td>0.80-1.00</td>
<td>.049</td>
</tr>
<tr>
<td>Asian</td>
<td>0.46</td>
<td>0.23-0.93</td>
<td>.03</td>
</tr>
<tr>
<td>Other</td>
<td>0.86</td>
<td>0.60-1.25</td>
<td>.44</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.33</td>
<td>1.22-1.46</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CHF</td>
<td>1.93</td>
<td>1.70-2.19</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>US resident</td>
<td>1.59</td>
<td>1.39-1.81</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CAGB or percutaneous coronary intervention</td>
<td>1.16</td>
<td>1.06-1.27</td>
<td>.002</td>
</tr>
<tr>
<td>Hypercholesterolemia*</td>
<td>0.81</td>
<td>0.75-0.89</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.27</td>
<td>1.14-1.42</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1.50</td>
<td>1.23-1.82</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Smoking (ever)</td>
<td>1.40</td>
<td>1.28-1.53</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>1.43</td>
<td>1.27-1.62</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>1.79</td>
<td>1.64-1.95</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

\( \text{CI} = \text{confidence interval; HR = hazard ratio; MI = myocardial infarction; CHF = congestive heart failure; CAGB = coronary artery bypass graft; TIA = transient ischemic attack.} \)

\( *\text{History of or currently taking antidiabetic or lipid-lowering medications.} \)
weight patients. Manson et al. found that excess body weight was directly related to all-cause mortality among the 115,195 women enrolled in the Nurses’ Health Study. Flegal et al. reported obesity to be associated with increased mortality in the participants of the National Health and Nutrition Examination Survey. However, these studies were performed in the general population.

Obesity Paradox in Cardiovascular Disease

In contrast with these epidemiologic studies, our analysis of the INVEST cohort suggests that among patients with a history of hypertension and coronary artery disease, overweight and class I to III obesity were associated with a decreased risk of morbidity and mortality compared with normal-weight patients, despite less blood pressure control. This finding is consistent with the notion of an “obesity paradox” that has been described in patients with documented cardiac disease (eg, heart failure), patients undergoing percutaneous coronary intervention, and patients with coronary artery disease referred for single photon emission computed tomography. In our analysis, overweight, class I, and class II to III obese patients with a history of congestive heart failure or percutaneous coronary intervention had a lower incidence of the primary outcome than normal-weight patients, similar to previous analyses. In a study of 7765 patients with heart failure enrolled in the Digitalis Investigation Group trial, overweight and obese patients had a relative risk reduction of 12% and 19%, respectively, for all-cause death compared with normal-weight patients. This is in concordance with our study that

Figure 4  Percentage of men to reach primary outcome according to BMI and age. BMI = body mass index.

Figure 5  Percentage of women to reach primary outcome according to BMI and age. BMI = body mass index.
showed overweight and obese patients with a history of congestive had a relative risk reduction of 20% and 24%, respectively, for the primary outcome. In a meta-analysis of 7290 patients undergoing percutaneous coronary intervention, overweight and obese patients had a relative risk reduction in death at 1 year of 36% and 27%, respectively. This is in concordance with our study that showed overweight and obese patients with a history of percutaneous coronary intervention had a relative risk reduction of 40% and 41%, respectively, for the primary outcome. However, some reports have questioned the existence of an obesity paradox; thus, it remains controversial. In our study group, thin patients (BMI <20 kg/m²) had the highest risk for the primary outcome, all-cause mortality, cardiovascular death, and nonfatal stroke compared with the normal-weight patients. Although thin patients at baseline were older and had a higher baseline incidence of renal insufficiency, heart failure, current smoking, previous myocardial infarction, stroke/TIA, and peripheral vascular disease, they had a higher risk for cardiovascular events in the multivariate model even after accounting for these differences. Whether low BMI itself is a risk factor for or a marker of severity of cardiovascular disease is unclear.

**Postulated Mechanisms for the Obesity Paradox in Patients with Cardiovascular Disease**

Several mechanisms could explain this paradox in patients with cardiovascular disease. First, studies have shown that normal-weight patients have a significantly higher percentage of high-risk coronary anatomy (left main disease or triple vessel disease) compared with obese patients. Coronary artery calcification area measured by electron-beam computed tomography was found to be significantly greater in overweight patients compared with obese patients. These findings provide a possible anatomic substrate for an obesity paradox. Second, leaner patients with heart failure have been shown to have increased levels of tumor necrosis factor and other inflammatory cytokines compared with obese patients. Adipose tissue has been shown to produce soluble tumor necrosis factor receptor that is thought to neutralize the deleterious effects of tumor necrosis factor-alpha on the myocardium, which may explain a protective effect of obesity in patients with heart failure. Third, obese patients display a readily identifiable phenotype that is believed to reflect a high risk for cardiovascular disease, and they may receive or seek treatment earlier in the course of disease, thereby altering the natural history of their disease when compared with lean patients (lead time bias). Fourth, it has been well documented that the hemodynamics of obesity hypertension are characterized by a high cardiac output, an expanded blood volume, and a lower systemic vascular resistance when compared with normal-weight patients. Because systemic resistance reflects the severity of hypertensive cardiovascular disease, the comparatively low values in obesity may translate into a better outcome in this population. Fifth, there are conflicting data whether obesity itself confers an increased risk for cardiovascular disease apart from its associated metabolic derangements. If these risk factors are well managed, such as hypertension and coronary artery disease, this may negate any increased risk associated with obesity. In the INVEST cohort, the blood pressure control was excellent and may negate the deleterious effects of obesity. Sixth, BMI itself has been questioned as the optimal measurement to use for assessing health risk associated with obesity. Other measures, such as waist-to-hip ratio and visceral fat measurement, may be better, and it has been postulated that “it is time to throw BMI out.” In some studies, BMI predicted mortality in women less well than in men. Ashton et al. found BMI to be a poor discriminator of cardiovascular heart disease risk in women compared with men despite a worse metabolic profile in those with increased BMI.

**Study Limitations**

This was a post hoc analysis and thus suffers from the limitations of such studies. Our conclusions should be considered to be hypothesis generating. The INVEST did not collect the waist-to-hip ratio data; therefore, we could not compare BMI with waist-to-hip ratio. Although we did find differences in the primary and secondary outcomes between BMI groups, the baseline characteristics of the BMI categories were not well matched. Although a stepwise model was used, the impact of these baseline differences cannot be ruled out.

**CONCLUSION**

In this well-treated hypertensive cohort with coronary artery disease, increasing BMI was associated with decreased morbidity and mortality when compared with normal-weight patients, consistent with an “obesity paradox.” Whether this relationship is the result of the shortcomings of BMI as a risk factor needs to be further elucidated.

**References**

CLINICAL RESEARCH STUDY

Clinical Characteristics of Patients with Acute Pulmonary Embolism: Data from PIOPED II

Paul D. Stein, MD, a,b Afzal Beemath, MD, a Fadi Matta, MD, a John G. Weg, MD, c Roger D. Yusen, MD, d Charles A. Hales, MD, e Russell D. Hull, MBBS, MSc, f Kenneth V. Leeper, Jr., MD, g H. Dirk Sostman, MD, h Victor F. Tapson, MD, i John D. Buckley, MD, j Alexander Gottschalk, MD, k Lawrence R. Goodman, MD, l Thomas W. Wakefield, MD, m Pamela K. Woodard, MD

a Department of Research, St. Joseph Mercy Oakland Hospital, Pontiac, Mich; b Department of Medicine, Wayne State University School of Medicine, Detroit, Mich; c Department of Medicine, University of Michigan, Ann Arbor; d Department of Medicine, Washington University School of Medicine, St. Louis, Mo; e Department of Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston; f Department of Medicine, University of Calgary, Calgary, Alberta, Canada; g Department of Medicine, Emory University, Atlanta, Ga; h Office of the Dean, Weill Cornell Medical College and Methodist Hospital, Houston, Tex; i Department of Medicine, Duke University, Durham, NC; j Department of Medicine, Henry Ford Hospital, Detroit, Mich; k Department of Radiology, Michigan State University, East Lansing; l Department of Radiology, Medical College of Wisconsin, Milwaukee; m Department of Surgery, University of Michigan, Ann Arbor; n Department of Radiology, Washington University, St. Louis, Mo.

ABSTRACT

BACKGROUND: Selection of patients for diagnostic tests for acute pulmonary embolism requires recognition of the possibility of pulmonary embolism on the basis of the clinical characteristics. Patients in the Prospective Investigation of Pulmonary Embolism Diagnosis II had a broad spectrum of severity, which permits an evaluation of the subtle characteristics of mild pulmonary embolism and the characteristics of severe pulmonary embolism.

METHODS: Data are from the national collaborative study, Prospective Investigation of Pulmonary Embolism Diagnosis II.

RESULTS: There may be dyspnea only on exertion. The onset of dyspnea is usually, but not always, rapid. Orthopnea may occur. In patients with pulmonary embolism in the main or lobar pulmonary arteries, dyspnea or tachypnea occurred in 92%, but the largest pulmonary embolism was in the segmental pulmonary arteries in only 65%. In general, signs and symptoms were similar in elderly and younger patients, but dyspnea or tachypnea was less frequent in elderly patients with no previous cardiopulmonary disease. Dyspnea may be absent even in patients with circulatory collapse. Patients with a low-probability objective clinical assessment sometimes had pulmonary embolism, even in proximal vessels.

CONCLUSION: Symptoms may be mild, and generally recognized symptoms may be absent, particularly in patients with pulmonary embolism only in the segmental pulmonary branches, but they may be absent even with severe pulmonary embolism. A high or intermediate-probability objective clinical assessment suggests the need for diagnostic studies, but a low-probability objective clinical assessment does not exclude the diagnosis. Maintenance of a high level of suspicion is critical. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Clinical diagnosis; Deep venous thrombosis; Pulmonary embolism; Venous thromboembolism

This study was supported by Grants HL63899, HL63928, HL63931, HL63932, HL63940, HL63941, HL63981, HL63982, and HL67453 from the U.S. Department of Health and Human Services, Public Health Services, National Heart, Lung, and Blood Institute, Bethesda, Maryland.

Requests for reprints should be addressed to Paul D. Stein, MD, St. Joseph Mercy Oakland, 44405 Woodward Ave., Pontiac, MI 48341-5023.

E-mail address: steinp@trinity-health.org

doi:10.1016/j.amjmed.2007.03.024
Acute pulmonary embolism in patients with severe or fatal pulmonary embolism at autopsy is generally unrecognized antemortem.1-4 Advances in the diagnostic methods for acute pulmonary embolism should affect this high rate of underdiagnosis.5-8 However, the successful use of diagnostic pathways requires recognition of patients with possible acute pulmonary embolism on the basis of the clinical characteristics.

The clinical characteristics of patients with acute pulmonary embolism in the first Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), an accuracy study of ventilation-perfusion scintigraphy, were described in all enrolled patients,9 patients with no previous cardiopulmonary disease,10 patients grouped according to the present syndromes of pulmonary embolism,11 and the elderly.12 One of the strengths of the data from PIOPED II is that many patients with mild pulmonary embolism were included, which permits the identification of subtle clinical characteristics. However, the clinical characteristics of patients with pulmonary embolism in PIOPED,9-12 as in PIOPED II and other investigations of patients enrolled in clinical trials,13,14 were sufficient to alert attuned physicians to the diagnosis and characteristics of patients who met the inclusion criteria. Patients who were too ill to participate, who died suddenly, or who were not identified because the clinical findings were mild or atypical were not included. With these constraints in mind, we describe the clinical characteristics of patients enrolled in PIOPED II.

**PATIENTS AND METHODS**

PIOPED II was a prospective multicenter investigation of multidetector computed-tomography angiography alone and combined with venous phase imaging of the pelvic and thigh veins for the diagnosis of acute pulmonary embolism.5 A composite reference test was used.5 Patients aged 18 years or more with clinically suspected acute pulmonary embolism were potentially eligible.5 Exclusion criteria included an inability to complete tests within 36 hours, critical illness, ventilatory support, shock, recent myocardial infarction, abnormal serum creatinine, allergy to contrast material, pregnancy, treatment with long-term anticoagulants, inferior vena cava filter, and deep venous thrombosis of the upper extremity.

To avoid confusing clinical findings of pulmonary embolism with comorbid conditions, we evaluated patients with no prior cardiopulmonary disease in addition to evaluating all patients. No prior cardiopulmonary disease was defined as no current asthma, pneumonia, history of chronic bronchitis, emphysema, chronic obstructive pulmonary disease, current or history of right or left-sided heart failure, lung cancer, or prior pulmonary embolism.

The circulatory collapse syndrome was defined as loss of consciousness or systolic blood pressure of 80 mm Hg or less. The hemoptysis/pleuritic pain syndrome (previously termed the pulmonary infarction syndrome)13 was defined as patients with either hemoptysis or pleuritic pain in the absence of circulatory collapse. The uncomplicated dyspnea syndrome was defined as dyspnea in the absence of hemoptysis, pleuritic pain, or circulatory collapse.

Measurements of arterial blood gases were obtained while the patient was breathing room air. The alveolar-arterial (A-a) oxygen difference was calculated as follows:15

\[
\text{A-a oxygen difference (mm Hg)} = 150 - 1.25 \times \frac{P_{\text{ACO}_2} - P_{\text{O}_2}}{H_11005}
\]

where \(P_{\text{ACO}_2}\) = partial pressure of carbon dioxide in arterial blood (mm Hg), and \(P_{\text{O}_2}\) = partial pressure of oxygen in arterial blood (mm Hg).

**Statistical Methods**

The chi-square test was used to compare the prevalence of clinical features in patients with and without pulmonary embolism. Because of the large number of comparisons, \(P\) values are underestimates. Comparisons of continuous variable means were made with the 2-tailed Student unpaired \(t\) test.

**RESULTS**

Acute pulmonary embolism was present in 192 patients, among whom 133 (69%) had no prior cardiopulmonary disease. Pulmonary embolism was excluded in 632 patients, among whom 366 (58%) had no prior cardiopulmonary disease.

**Syndromes of Pulmonary Embolism**

The syndrome of hemoptysis or pleuritic pain occurred in 41% of patients with no prior cardiopulmonary disease and in 44% of all patients with pulmonary embolism (Table 1). The uncomplicated dyspnea syndrome occurred in 36% of patients with no prior cardiopulmonary disease and in 36% of all patients with pulmonary embolism. The circulatory collapse syndrome was uncommon: 8% in patients with no prior cardiopulmonary disease and 8% in all enrolled patients with acute pulmonary embolism. The presentations of 19 patients (14%) with pulmonary embolism and no prior cardiopulmonary disease differed from these syndromes. The presenting findings in some of these patients were

**CLINICAL SIGNIFICANCE**

- In patients with pulmonary embolism only in the segmental pulmonary branches, generally recognized symptoms may be mild or absent, leading to underdiagnosis.
- Absence of symptoms is most common in patients with pulmonary embolism only in the segmental pulmonary branches, but this also occurs in patients with proximal pulmonary embolism.
- A low-probability objective clinical assessment does not exclude pulmonary embolism, even in the proximal pulmonary arteries.
tachypnea, tachycardia, or a PaO₂ less than 80 mm Hg with signs or symptoms of deep venous thrombosis (Table 1).

### Partial Pressure of Oxygen in Arterial Blood and Alveolar-Arterial Oxygen Difference

The partial pressure of oxygen in arterial blood (PaO₂) while breathing room air was measured in 74 patients with pulmonary embolism and in 48 patients with pulmonary embolism and no prior cardiopulmonary disease (Table 2). The PaO₂ while breathing room air was 80 mm Hg or more in 32% of all patients with pulmonary embolism and 80 mm Hg or more in 38% of patients with no prior cardiopulmonary disease. The A-a oxygen difference was 20 mm Hg or less in 32% of all patients with pulmonary embolism and in 35% of patients with pulmonary embolism and no prior cardiopulmonary disease (Table 2).

### Risk Factors for Pulmonary Embolism

Immobilization (bed rest within past month for the most of the day for ≥ 3 consecutive days) was the most frequent risk factor.

---

### Table 1  Syndromes of Acute Pulmonary Embolism

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>PE All Patients</th>
<th>No PE All Patients</th>
<th>PE No Prior CPD</th>
<th>No PE No Prior CPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoptysis or pleuritic pain</td>
<td>32 (44)</td>
<td>20 (44)</td>
<td>17 (35)</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Uncomplicated dyspnea</td>
<td>38 (50)</td>
<td>25 (50)</td>
<td>13 (25)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Circulatory collapse</td>
<td>24 (32)</td>
<td>13 (32)</td>
<td>8 (16)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Different presentation</td>
<td>29 (40)</td>
<td>22 (40)</td>
<td>14 (27)</td>
<td>7 (16)</td>
</tr>
</tbody>
</table>

CPD = cardiopulmonary disease; PE = pulmonary embolism.

* P < .05.
† P < .025.
‡ P < .01.
§ P < .001.

### Table 2  Arterial Blood Gases and Alveolar-Arterial Oxygen Difference While Breathing Room Air

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>PE All Patients</th>
<th>No PE All Patients</th>
<th>PE No Prior CPD</th>
<th>No PE No Prior CPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 40</td>
<td>17 (9)</td>
<td>17 (9)</td>
<td>4 (5)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>50-59</td>
<td>32 (17)</td>
<td>32 (17)</td>
<td>12 (16)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>60-69</td>
<td>35 (19)</td>
<td>35 (19)</td>
<td>20 (27)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>70-79</td>
<td>32 (17)</td>
<td>32 (17)</td>
<td>14 (19)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>70 (38)</td>
<td>70 (38)</td>
<td>24 (32)</td>
<td>24 (32)</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 35</td>
<td>65 (35)‡</td>
<td>65 (35)‡</td>
<td>42 (57)</td>
<td>42 (57)</td>
</tr>
<tr>
<td>36-39</td>
<td>39 (21)</td>
<td>39 (21)</td>
<td>18 (24)</td>
<td>18 (24)</td>
</tr>
<tr>
<td>≥ 40</td>
<td>82 (44)§</td>
<td>82 (44)§</td>
<td>39 (21)</td>
<td>39 (21)</td>
</tr>
<tr>
<td>pH (units)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 7.35</td>
<td>13 (7)†</td>
<td>13 (7)†</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>7.35-7.45</td>
<td>131 (70)†</td>
<td>131 (70)†</td>
<td>41 (55)</td>
<td>41 (55)</td>
</tr>
<tr>
<td>&gt; 7.45</td>
<td>42 (23)§</td>
<td>42 (23)§</td>
<td>33 (45)</td>
<td>33 (45)</td>
</tr>
<tr>
<td>A-a O₂ difference (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 20</td>
<td>70 (38)</td>
<td>70 (38)</td>
<td>24 (32)</td>
<td>24 (32)</td>
</tr>
<tr>
<td>21-30</td>
<td>32 (17)</td>
<td>32 (17)</td>
<td>10 (11)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>31-40</td>
<td>30 (16)</td>
<td>30 (16)</td>
<td>18 (24)</td>
<td>18 (24)</td>
</tr>
<tr>
<td>41-50</td>
<td>32 (17)</td>
<td>32 (17)</td>
<td>14 (19)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>51-60</td>
<td>17 (9)</td>
<td>17 (9)</td>
<td>10 (14)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>≥ 61</td>
<td>5 (3)</td>
<td>5 (3)</td>
<td>3 (4)</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

CPD = cardiopulmonary disease; PE = pulmonary embolism.

* P < .05.
† P < .025.
‡ P < .01.
§ P < .001.
factor assessed in patients with pulmonary embolism, and surgery was the usual cause of immobilization (Table 3). One or more of the assessed risk factors were reported in 92% of patients with pulmonary embolism and no prior cardiopulmonary disease. Among all patients with pulmonary embolism, 94% had 1 or more of the assessed risk factors.

### Symptoms of Pulmonary Embolism

New dyspnea at rest or on exertion was the most frequent symptom in patients with pulmonary embolism and no prior cardiopulmonary disease (73%) (Table 4). Dyspnea only on exertion was observed in 16% of patients with pulmonary embolism and no prior cardiopulmonary disease and in 16% of all patients with pulmonary embolism (Table 5). The onset was within seconds, minutes, or hours in 83% of patients with pulmonary embolism and no prior cardiopulmonary disease and in 87% of all patients with pulmonary embolism. In some, however, the onset of dyspnea occurred over days.

Pleuritic chest pain was more frequent than hemoptysis (Table 4). Cough, when present, was usually nonproductive, but purulent sputum and clear sputum also were reported. Hemoptysis may have been pinkish, blood streaked, or all blood. Hemoptysis of pure blood occurred in only 1 patient with pulmonary embolism and no prior cardiopulmonary disease, and it was less than 1 teaspoonful. Thigh pain and swelling were rarely described in the absence of calf pain or swelling.

### Signs of Pulmonary Embolism

Tachypnea was present in approximately one half of the patients with pulmonary embolism (Table 6). Tachycardia was present in approximately one fourth. Clinical evidence of pulmonary hypertension (accentuated pulmonary component of the second sound), right ventricular pressure overload or enlargement (right ventricular lift), or elevated right atrial pressure (jugular venous distension) was shown in
21% of patients with no prior cardiopulmonary disease and in 22% of all patients with pulmonary embolism. Lung examination was abnormal in 29% of patients with pulmonary embolism and no prior cardiopulmonary disease and in 37% of all patients with pulmonary embolism. Crackles and decreased breath sounds were the most frequent lung findings. Rhonchi and wheezes occurred uncommonly. Signs of deep venous thrombosis (edema, erythema, tenderness, or palpable cord) in the thigh, in the absence of deep venous thrombosis in the calf, were rare (Table 6). Among all patients with pulmonary embolism, calf swelling plus pain with palpation of the deep veins occurred in 32%.

### Table 4 Symptoms of Pulmonary Embolism

<table>
<thead>
<tr>
<th></th>
<th>PE No Prior CPD</th>
<th>No PE No Prior CPD</th>
<th>PE All Patients</th>
<th>No PE All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>127-133</td>
<td>361-366</td>
<td>184-191</td>
<td>622-632</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dyspnea**
- Dyspnea (rest or exertion) 97 (73) 248 (68) 151 (79) 459 (73)
- Dyspnea (at rest)# 73 (55) 167 (46) 117 (61) 338 (54)
- Dyspnea (exertion only)# 21 (16) 73 (20) 31 (16) 111 (18)
- Orthopnea (=2-pillow) 37 (28) 88 (24) 69 (36) 220 (35)

**Pleuritic pain** 58 (44) 207 (57) 89 (47) 376 (59)

**Chest pain (not pleuritic)** 25 (19) 80 (22) 33 (17) 130 (21)

**Cough** 45 (34)* 103 (28)** 82 (43)† 248 (39)††

**Wheezeing** 27 (21) 66 (18) 58 (31) 193 (31)

**Calf or thigh swelling** 52 (41) 62 (17)√ 72 (39) 126 (20)√

**Calf and thigh swelling** 9 (7) 14 (4) 15 (8) 35 (6)

**Calf or thigh pain** 56 (44) 83 (23)√ 78 (42) 156 (25)√

**Calf and thigh pain** 22 (17) 24 (7)√ 30 (16) 61 (10)√

CPD = cardiopulmonary disease; PE = pulmonary embolism.
*Hemoptysis, PE, no CPD: 2 = slightly pinkish, 4 = blood-streaked, 1 = all blood (<1 tsp).
**Hemoptysis, no PE, no CPD: 1 = slightly pink, 2 = streaked, 7 = all blood (1 patient, too little to quantify; 1 patient, <1 tsp; 4 patients, 1 tsp to ½ cup; 1 patient, >½ cup).
†Hemoptysis, PE, all patients: 3 = slightly pinkish, 6 = blood-streaked, 2 = all blood (<1 tsp).
††Hemoptysis, No PE, all patients: 7 = slightly pinkish, 9 = blood streaked, 9 = all blood (1 patient, too little to quantify; 3 patients, <1 tsp; 4 patients, 1 tsp to ½ cup; 1 patient, >½ cup).
#Information not available in some.
*P < .01.
**P < .001.
††P < .025.

### Table 5 Rate of Onset of Dyspnea

<table>
<thead>
<tr>
<th></th>
<th>Patients with Dyspnea and PE No Prior CPD</th>
<th>Patients with Dyspnea and No PE No Prior CPD</th>
<th>All Patients with Dyspnea and PE</th>
<th>All Patients with Dyspnea and No PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>92</td>
<td>242</td>
<td>143</td>
<td>450</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Seconds** 42 (46) 109 (45) 59 (41) 206 (46)

**Minutes** 24 (26) 69 (29) 37 (26) 117 (26)

**Hours** 10 (11) 35 (14) 20 (14) 70 (16)

**Days** 16 (17) 29 (12) 27 (19) 57 (13)

CPD = cardiopulmonary disease; DVT = deep vein thrombosis; PE = pulmonary embolism.
All differences not significant.

### Combinations of Signs and Symptoms

Either dyspnea or tachypnea was present in 84% of patients with pulmonary embolism and no prior cardiopulmonary disease, and in 86% of all patients with pulmonary embolism. Dyspnea, tachypnea, or pleuritic pain was present in 92% of patients with pulmonary embolism and no prior cardiopulmonary disease and in 92% of all patients with pulmonary embolism. One or more of these signs and symptoms or signs of deep venous thrombosis were present in 98% of patients with pulmonary embolism and no prior cardiopulmonary disease, and in 97% of all patients with pulmonary embolism.
Patients with Circulatory Collapse
Among patients with circulatory collapse with pulmonary embolism and no prior cardiopulmonary disease, dyspnea was present in 9 of 11 (82%), dyspnea or tachypnea was present in 10 of 11 (91%), and dyspnea, tachypnea, or pleuritic pain was present in 10 of 11 (91%). All 11 patients had dyspnea, tachypnea, pleuritic pain, or signs of deep venous thrombosis.

Among all patients with circulatory collapse and pulmonary embolism, dyspnea was present in 13 of 15 (87%), dyspnea or tachypnea was present in 14 of 15 (93%), and dyspnea, tachypnea, or pleuritic pain was present in 14 of 15 (93%). All 15 patients had dyspnea, tachypnea, pleuritic pain, or signs of deep venous thrombosis.

Clinical Characteristics According to Location of Pulmonary Embolism
Among 150 patients with pulmonary embolism in whom images were classifiable, main or lobar (proximal) pulmonary arteries showed pulmonary embolism by computed tomography angiography in 116 (77%). The largest affected branch was segmental in 32 patients (21%) and subsegmental in 2 patients (1%). Among all patients with pulmonary embolism in proximal arteries, 94% presented one of the typical syndromes (hemoptysis/pleuritic pain syndrome, uncomplicated dyspnea syndrome, or circulatory collapse syndrome), whereas in patients with segmental pulmonary embolism, only 72% had one of these presentations. The others with segmental emboli had only calf swelling.

Dyspnea or tachypnea occurred in 92% of all patients with pulmonary embolism in whom the pulmonary embolism was proximal, but in only 65% with segmental pulmonary embolism. Dyspnea, tachypnea, or pleuritic pain occurred in 97% of patients with proximal pulmonary embolism and in 77% of patients with segmental pulmonary embolism. Dyspnea at rest or during exertion, dyspnea at rest, orthopnea, tachypnea, and Paco2 of 35 mm Hg or less were more frequent in patients with proximal pulmonary embolism, and Paco2 of 40 mm Hg or more was less frequent than in patients with segmental pulmonary embolism.

Table 6 Signs of Pulmonary Embolism

<table>
<thead>
<tr>
<th></th>
<th>PE No Prior CPD</th>
<th>No PE No Prior CPD</th>
<th>PE All Patients</th>
<th>No PE All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td><strong>n (%)</strong></td>
<td><strong>n (%)</strong></td>
<td><strong>n (%)</strong></td>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachypnea (&gt;20/min)</td>
<td>71 (54)</td>
<td>155 (43)#</td>
<td>108 (57)</td>
<td>296 (47)$</td>
</tr>
<tr>
<td>Tachycardia (&gt;100/min)</td>
<td>32 (24)</td>
<td>52 (14)$</td>
<td>49 (26)</td>
<td>98 (16)$</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>3 (2)</td>
<td>27 (7)**</td>
<td>8 (4)</td>
<td>40 (6)</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>0 (0)</td>
<td>1 (0.003)</td>
<td>1 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Temperature &gt;38.5°C (&gt;101.3°F)</td>
<td>1 (1)</td>
<td>12 (3)</td>
<td>3 (2)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Cardiac examination (abnormal)</td>
<td>28 (21)</td>
<td>39 (11)$</td>
<td>42 (22)</td>
<td>72 (12)$</td>
</tr>
<tr>
<td>Increased P2†</td>
<td>15 (15)</td>
<td>14 (5)$</td>
<td>22 (15)</td>
<td>27 (5)$</td>
</tr>
<tr>
<td>Right ventricular lift‡</td>
<td>4 (4)</td>
<td>6 (2)</td>
<td>8 (5)</td>
<td>9 (2)$</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>18 (14)</td>
<td>27 (8)**</td>
<td>25 (13)</td>
<td>50 (8)**</td>
</tr>
<tr>
<td>Lung examination (abnormal)</td>
<td>38 (29)</td>
<td>94 (26)</td>
<td>70 (37)</td>
<td>227 (36)</td>
</tr>
<tr>
<td>Rales (crackles)</td>
<td>23 (18)</td>
<td>52 (14)</td>
<td>40 (21)</td>
<td>112 (18)</td>
</tr>
<tr>
<td>Wheezes</td>
<td>2 (2)</td>
<td>12 (3)</td>
<td>6 (3)</td>
<td>54 (9)$</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>2 (2)</td>
<td>8 (2)</td>
<td>9 (5)</td>
<td>32 (5)</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td>22 (17)</td>
<td>42 (12)</td>
<td>40 (21)</td>
<td>109 (17)</td>
</tr>
<tr>
<td>Pleural friction rub</td>
<td>0 (0)</td>
<td>3 (1)</td>
<td>2/ (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>DVT signs††</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calf or thigh</td>
<td>62 (47)*</td>
<td>77 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calf and thigh</td>
<td>18 (14)</td>
<td>16 (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CPD = cardiopulmonary disease; PE = pulmonary embolism; P2 = pulmonary component of second sound; DVT = deep venous thrombosis.
*Number of patients with PE and no CPD who had 1 or more signs of DVT: edema = 55, erythema = 5, tenderness = 32, palpable cord = 2.
†Data in 103 patients with PE and no CPD, 293 with no PE and no CPD, 145 with PE all patients, 512 no PE all patients.
‡Data in 110 patients with PE and no CPD, 301 with no PE and no CPD, 155 with PE all patients, 529 no PE all patients.
§P <.01.
‖P < .001.
¶P < .0001.
#P < .05.
**P < .05.
††Edema, erythema, tenderness, or palpable cord.
(Tables 7 to 10). In patients with no prior cardiopulmonary disease and in all patients with pulmonary embolism, the combination of dyspnea or tachypnea occurred less frequently in elderly patients than in younger patients.

**Objective Clinical Assessment in Patients with Pulmonary Embolism**

The majority of patients with pulmonary embolism (113/176, 64%) had a moderate probability of pulmonary embolism by the Wells clinical scoring system. The remaining 176 patients (64%) had a low-probability objective clinical assessment by the Wells scoring system. The remaining patients with pulmonary embolism were equally divided between age groups. Comparable proportions were found among patients with no prior cardiopulmonary disease, elderly patients, younger patients, and patients who presented with the various syndromes. Among patients with pulmonary embolism in the main or lobar pulmonary arteries in whom an objective clinical assessment was recorded, 16 of 107 (15%) had a low-probability objective clinical assessment by the Wells scoring system.

**Table 7** Symptoms in Patients with Pulmonary Embolism and No Preexisting Cardiac or Pulmonary Disease According to Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Symptoms in Patients with Pulmonary Embolism and No Preexisting Cardiac or Pulmonary Disease According to Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70 Y</td>
<td>&lt;70 Y</td>
</tr>
<tr>
<td>N = 33-35</td>
<td>N = 93-98</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td>Dyspnea (rest or exertion)</td>
<td>23 (66)</td>
</tr>
<tr>
<td>Dyspnea (at rest)*</td>
<td>17 (49)</td>
</tr>
<tr>
<td>Dyspnea (exertion only)*</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Orthopnea (≥2-pillow)</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Pleuritic pain</td>
<td>12 (35)</td>
</tr>
<tr>
<td>Chest pain (not pleuritic)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Cough</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Calf or thigh swelling</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Calf or thigh pain</td>
<td>9 (26)</td>
</tr>
</tbody>
</table>

*Information not available in some.
†P < .05 age ≥ 70 years vs < 70 years. All other differences between age groups are not significant.

**Table 8** Symptoms in All Patients with Pulmonary Embolism According to Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Symptoms in All Patients with Pulmonary Embolism According to Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70 Y</td>
<td>&lt;70 Y</td>
</tr>
<tr>
<td>N = 53-55</td>
<td>N = 130-137</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td>Dyspnea (rest or exertion)</td>
<td>41 (75)</td>
</tr>
<tr>
<td>Dyspnea (at rest)*</td>
<td>33 (60)</td>
</tr>
<tr>
<td>Dyspnea (exertion only)*</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Orthopnea (≥2-pillow)</td>
<td>17 (31)</td>
</tr>
<tr>
<td>Pleuritic pain</td>
<td>18 (33)</td>
</tr>
<tr>
<td>Chest pain (not pleuritic)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Cough</td>
<td>24 (44)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Calf or thigh swelling</td>
<td>14 (26)</td>
</tr>
<tr>
<td>Calf or thigh pain†</td>
<td>15 (28)</td>
</tr>
</tbody>
</table>

*Information not available in some.
†P < .025 age ≥ 70 years vs < 70 years. All other differences between age groups are not significant.

**Table 9** Signs in Patients with Pulmonary Embolism and No Preexisting Cardiac or Pulmonary Disease According to Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Signs in Patients with Pulmonary Embolism and No Preexisting Cardiac or Pulmonary Disease According to Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70 Y</td>
<td>&lt;70 Y</td>
</tr>
<tr>
<td>N = 33-35</td>
<td>N = 93-98</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Tachypnea (≥20 min)</td>
<td>16 (47)</td>
</tr>
<tr>
<td>Tachycardia (&gt;100 min)</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Temperature &gt; 38.5°C (&gt;101.3°F)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cardiac examination (any)</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Increased P2*</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Right ventricular lift†</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Lung examination (any)</td>
<td>15 (43)</td>
</tr>
<tr>
<td>Wheezes</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Pleural friction rub</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Data in 26 patients ≥ 70 years, 77 patients < 70 years.
†Data in 30 patients ≥ 70 years, 80 patients < 70 years.
‡P < .05 age ≥ 70 years vs < 70 years. All other differences between age groups are not significant.

**Table 10** Signs in All Patients with Pulmonary Embolism

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Signs in All Patients with Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70 Y</td>
<td>&lt;70 Y</td>
</tr>
<tr>
<td>N = 52-55</td>
<td>N = 130-137</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Tachypnea (≥20 min)</td>
<td>28 (51)</td>
</tr>
<tr>
<td>Tachycardia (&gt;100 min)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Temperature &gt; 38.5°C (&gt;101.3°F)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cardiac examination (any)</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Increased P2*</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Right ventricular lift†</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>10 (19)</td>
</tr>
<tr>
<td>Lung examination (any)</td>
<td>25 (45)</td>
</tr>
<tr>
<td>Wheezes</td>
<td>14 (26)</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Pleural friction rub</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*Data in 42 patients ≥ 70 years, 103 patients < 70 years.
†Data in 45 patients ≥ 70 years, 110 patients < 70 years.

All differences between age groups not significant.

*Information not available in some.
†P < .05 age ≥ 70 years vs < 70 years. All other differences between age groups are not significant.
DISCUSSION

The data show a broad range of severity of clinical findings in patients with pulmonary embolism. The syndrome of pleuritic pain or hemoptysis, in the absence of circulatory collapse, was the most frequent mode of presentation in PIOPED, occurring in 65% of patients with pulmonary embolism and no prior cardiopulmonary disease. The present data from PIOPED II showed somewhat fewer patients with pleuritic pain or hemoptysis, and more had the uncomplicated dyspnea syndrome. Circulatory collapse was an uncommon mode of presentation in PIOPED and PIOPED II because of selection criteria. Patients with hemoptysis or pleuritic pain syndrome have been shown to have less severe pulmonary embolism than patients with uncomplicated dyspnea according to an objective pulmonary angiography scoring system. Patients with circulatory collapse had the most severe pulmonary embolism based on the angiographic score, but the score was not statistically significantly more than in patients with uncomplicated dyspnea. The absence of dyspnea did not exclude pulmonary embolism, even in patients with circulatory collapse.

Typically, among patients with acute pulmonary embolism, the PaO₂ is low. However, acute pulmonary embolism cannot be excluded on the basis of a normal PaO₂. This was shown in the present study and in PIOPED, in which 26% of such patients with acute pulmonary embolism and no prior cardiopulmonary disease who had measurements of the PaO₂ while breathing room air had a PaO₂ of 80 mm Hg or more. Even among patients with submassive or massive acute pulmonary embolism in the Urokinase Pulmonary Embolism Trial, 12% had a PaO₂ of 80 mm Hg or more.

In patients with pulmonary embolism breathing room air, the A-a oxygen difference closely correlates with the PaO₂ and has no greater diagnostic value.

The present data show that patients with pulmonary embolism may have dyspnea only on exertion. Orthopnea also was shown to be a symptom of pulmonary embolism. Orthopnea occurred in patients with pulmonary embolism who had dyspnea only on exertion and in those with dyspnea at rest. Typically, the onset of dyspnea occurred over seconds, minutes, or hours, but in some it occurred over days. Compared with patients who had only segmental pulmonary artery pulmonary embolism, patients with proximal pulmonary embolism (main or lobar pulmonary embolism) more often had typical signs, symptoms, and blood gases. Patients with pulmonary embolism even in the main or lobar pulmonary arteries may have a low-probability objective clinical assessment.

In both PIOPED and PIOPED II, pleuritic chest pain was more frequent in patients with pulmonary embolism than hemoptysis. Hemoptysis, when present, occurred only in small amounts. Examination of the lungs was abnormal in a minority (29% with no prior cardiopulmonary disease) of patients with pulmonary embolism.

Signs of deep venous thrombosis in patients with no prior cardiopulmonary disease were more frequent in PIOPED II than in PIOPED (47% vs 11%), as were symptoms of deep venous thrombosis (44% vs 26%). However, in PIOPED II the frequency of signs of deep venous thrombosis (41%) and symptoms of deep venous thrombosis (39%) were similar to those in the Urokinase Pulmonary Embolism Trial.

Dyspnea, tachypnea, pleuritic pain, or signs of deep venous thrombosis were seen in the majority of patients with pulmonary embolism in PIOPED and in the present data from PIOPED II. Conversely, in the absence of dyspnea, tachypnea, pleuritic pain, or signs of deep venous thrombosis, pulmonary embolism was infrequently diagnosed.

The diagnosis of pulmonary embolism among elderly patients has been thought to be particularly difficult because the expected signs and symptoms may be absent or ignored. This did not seem to be the case in the experience of PIOPED or in the present experience of PIOPED II, although among patients with pulmonary embolism the combination of dyspnea or tachypnea was present in fewer elderly patients than younger patients. In the absence of dyspnea or tachypnea among elderly patients in PIOPED, unexplained radiographic abnormalities were important diagnostic clues. When the diagnosis of pulmonary embolism is uncertain, computed tomography angiography can be performed with the same sensitivity and specificity in elderly patients as in younger patients, although renal failure was a problem among elderly patients who underwent conventional angiography.

CONCLUSIONS

Symptoms may be mild and generally recognized symptoms may be absent in patients with the largest pulmonary embolism in the segmental pulmonary branches, but typical symptoms may be absent even in patients with large emboli. A high or intermediate-probability objective clinical assessment may suggest the need for diagnostic studies, but a low-probability objective clinical assessment was sometimes present, even in patients with proximal pulmonary embolism. Maintenance of a high level of suspicion is critical for the identification of patients in whom diagnostic tests may be necessary.

ACKNOWLEDGMENT

Nikunj R. Patel, MD, assisted in analyzing the data.

References


Thyroid Function Abnormalities during Amiodarone Therapy for Persistent Atrial Fibrillation

Elizabeth L. Batcher, MD,a X. Charlene Tang, MD, PhD,b Bramah N. Singh, MD, DSc,a Steven N. Singh, MD,c Domenic J. Reda, PhD,b Jerome M. Hershman, MDa for the SAFE-T Investigators

aWest Los Angeles Veterans Affairs Medical Center, Los Angeles, Calif, bEdward Hines, Jr. Veterans Affairs Hospital, Hines, Ill, and cDepartment of Veterans Affairs Medical Center, Washington, DC.

ABSTRACT

BACKGROUND: Many patients receiving amiodarone therapy are male. The long-term risk for amiodarone-induced thyroid dysfunction in these patients has not been systematically and prospectively investigated. The purpose of this study was to determine the extent of amiodarone-induced thyroid dysfunction in a large male cohort.

METHODS: This is a substudy of a prospective randomized controlled trial (SAFE-Trial) in which amiodarone, sotalol, and placebo for persistent atrial fibrillation were evaluated. For the purpose of this substudy, sotalol and placebo groups were combined into a control group. Serial thyroid function tests were performed over 1-4.5 years. Of the 665 patients enrolled in the SAFE-Trial, 612 patients were included in this sub-study.

RESULTS: Subclinical hypothyroidism, thyroid-stimulating hormone (TSH) level 4.5-10 mU/L, was seen among 25.8% of the amiodarone-treated patients and only 6.6% of controls (P < .0001). Overt hypothyroidism, TSH level >10 mU/L, was seen among 5.0% of the amiodarone-treated patients, and only 0.3% of controls (P < .001). By 6 months, 93.8% of the patients who developed TSH elevations above 10 mU/L on amiodarone had been detected. There was a trend toward a greater proportion of hyperthyroidism, defined as a TSH <0.35 mU/L, in the amiodarone group compared with the control group (5.3% vs 2.4%, P = .07).

CONCLUSIONS: Hypothyroidism developed in 30.8% of older males treated with amiodarone and in only 6.9% of the controls. Hypothyroidism presented at an early stage of therapy. Hyperthyroidism occurred in 5.3% of amiodarone treated patients, and was a subclinical entity in all but 1 case. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Amiodarone; Hypothyroidism; Sotalol; Thyroid

Although the unique pharmacologic properties of amiodarone and its varied clinical uses have been known for several decades, its unparalleled effectiveness in maintaining sinus rhythm has emerged only in recent years. The drug’s major shortcoming has been its propensity to induce disorders of thyroid function. It causes various forms of thyroid dysfunction ranging from elevated serum thyroxine (T4) levels and low triiodothyronine (T3) levels in euthyroid patients to overt hypothyroidism or hyperthyroidism. The primary cause of the thyroid dysfunction is the large iodine load that can cause either hypothyroidism or hyperthyroidism. Hyperthyroidism can also be caused by a thyroiditis that is iodine-independent, and known as type 2 hyperthyroidism. Studies examining the prevalence of amiodarone-induced thyroid dysfunction vary in regard to geographic location and iodine intake, ratio of women to men, and length of follow-up. Most studies have shown a trend toward more frequent hypothyroidism in iodine-sufficient areas, such as the
United States, and more frequent thyrotoxicosis in iodine-deficient areas, such as Italy. In general, amiodarone-induced thyroid dysfunction is more common in patients with an underlying thyroid disorder. Rates of thyroid dysfunction have been reported to be 14%-18%, with the highest prevalence among women and those with antithyroid antibodies.

The data reported in this article deal with thyroid dysfunction in a large cohort of male patients treated with amiodarone and compared with a control group stemming from a substudy of the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T). The objective of the substudy was to determine the incidence of hypothyroidism, defined as thyroid-stimulating hormone (TSH) >4.5 mU/L, or hyperthyroidism, defined as TSH <0.35 mU/L, induced by amiodarone and compared with sotalol and placebo as the control.

METHODS

Study Design

The details of the study (SAFE-T) design from which the data for the current report are derived have been reported previously. In brief, patients with persistent atrial fibrillation (AF) were randomly assigned to amiodarone, sotalol, or placebo after optimal anticoagulation (international normalized ratio ranging from 2 to 3). After 4 weeks of therapy, those not in sinus rhythm (SR) had their AF electrically cardioverted. Once SR was achieved, anticoagulation was continued for at least 8 weeks. Recurrence of AF was documented by weekly transtelephonic monitoring. All patients were followed for at least 1 year regardless of their rhythm status. Patients remaining in SR were maintained on open-label medications with continued follow-up to 1 year. Thyroid function was examined at baseline, 3 months, 6 months, and at every 6 months thereafter by measurement of serum thyrotropin (TSH) concentration. Free T4 and total T3 levels were not consistently obtained.

Statistical Analysis

Incidence rates of hypothyroidism and hyperthyroidism between groups were compared using chi-squared test, or Fisher’s exact test as appropriate. Logistic regression was used to calculate odds ratios. An alpha value of .05 or less was considered to indicate statistical significance. All statistical tests reported were 2-sided. All analyses were performed using SAS version 8.0 (SAS Institute Inc., Cary, NC).

RESULTS

Patients

A total of 665 patients with persistent atrial fibrillation were enrolled in the SAFE trial. There were 267 patients in the amiodarone group, 261 in the sotalol group, and 137 in the placebo group. For this study, 53 patients were excluded due to the lack of TSH values at either baseline or during follow-up. The sotalol and placebo groups were combined to form the control group, as neither placebo nor sotalol would be expected to alter thyroid function.

Table 1 shows the baseline characteristics of the patients in the amiodarone and control groups. Overall, 607 of 612 patients (99%) were male and 5 (0.8%) were female; mean age was 67.0 (±9.3) years. Ninety percent of the patients were white and 5.7% were black, without statistical differences in ethnic breakdown between the groups. There were no significant differences in the prevalence of diabetes, ischemic heart disease, smoking, or baseline TSH level between the groups. Rates of baseline levothyroxine therapy were similar between the control and amiodarone-treated groups, 1.4% versus 2.8%, respectively (P = .20). The pairwise comparisons showed that there were no statistical differences in baseline TSH between original treatment groups.

Sixty-six of 365 patients in the control group received open-label amiodarone for at least 1 month during follow-up and were excluded from the outcome analysis in

CLINICAL SIGNIFICANCE

- Nearly one third of older men treated with amiodarone for persistent atrial fibrillation developed some degree of hypothyroidism, compared with 6.9% of those treated with sotalol or placebo.
- Amiodarone treatment also was associated with a slight, nonsignificant increase in hyperthyroidism (5.3% vs 2.4%).
- During amiodarone therapy, all patients should be carefully monitored for both hypothyroidism and hyperthyroidism.
- Amiodarone-induced overt hypothyroidism generally warrants levothyroxine treatment.
Table 2, Figure 1, and Figure 2. Those with open-label amiodarone tended to be younger (64.8 ± 9.3 years) and had a higher body mass index (33.9 ± 6.1 kg/m²) compared with the remaining 299 patients in the control group (P < .04, P = .002, respectively). There were no significant differences in other demographic and clinical characteristics between the patients with open-label amiodarone and the remaining patients in the control group.

### Incidence of Hyperthyroidism and Hypothyroidism During Follow-up

<table>
<thead>
<tr>
<th>TSH Level (mU/L)</th>
<th>Amiodarone Group</th>
<th>Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 247</td>
<td>n = 299</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(TSH &lt; 0.35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.3 (13)</td>
<td>2.4 (7)</td>
<td>.07</td>
</tr>
<tr>
<td>No</td>
<td>94.7 (232)</td>
<td>97.6 (291)</td>
<td></td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>(TSH &gt; 4.5-10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25.8 (62)</td>
<td>6.6 (19)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No</td>
<td>74.2 (178)</td>
<td>93.4 (271)</td>
<td></td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>(TSH &gt; 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.0 (12)</td>
<td>0.3 (1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>95.0 (228)</td>
<td>99.7 (289)</td>
<td></td>
</tr>
</tbody>
</table>

TSH = thyroid-stimulating hormone.
*Excluding 66 patients with open-label amiodarone from the control group.
†Four patients who had low TSH at both baseline and follow-up were excluded from analysis.
‡Twenty patients who had elevated TSH at both baseline and follow-up were excluded from analysis.

**Figure 1** Figure reflects an updated analysis in which 66 patients with open-label amiodarone were excluded from the control group. Odds ratio (OR) and 95% confidence limits of hypothyroidism (TSH > 4.5 mU/L) in the amiodarone group compared with the control group. Overall, patients on amiodarone had a higher likelihood to develop hypothyroidism than those on placebo or sotalol. As hypothesized, there was no significant difference in the incidence of hypothyroidism between the sotalol- and placebo-treated patients (data not shown).

**Figure 2** Figure reflects an updated analysis in which 66 patients with open-label amiodarone were excluded from the control group. Rate of hypothyroidism (TSH > 4.5 mU/L) for the amiodarone and control groups at 3, 6, 12, and > 12 months follow-up.

### Incidence of Hypothyroidism and Hyperthyroidism

Table 2 presents the incidence of hypothyroidism and hyperthyroidism for patients in the amiodarone group and the control group. An elevation in TSH was classified into 2 levels: subclinical hypothyroidism, TSH < 4.5 mU/L; and overt hypothyroidism, TSH > 10 mU/L. There was a higher incidence of subclinical hypothyroidism (25.8%) in the amiodarone group compared with the control group (6.6%) (P < .0001). An elevation of TSH > 10 mU/L was seen among 5.0% of the amiodarone-treated patients and only 0.3% of controls (P < .001), indicating that the patients on amiodarone were more likely to develop overt hypothyroidism than those on placebo or sotalol. As hypothesized, there was no significant difference in the incidence of hypothyroidism between the sotalol- and placebo-treated patients (data not shown).

Table 2, Figure 1, and Figure 2. Those with open-label amiodarone tended to be younger (64.8 ± 9.3 years) and had a higher body mass index (33.9 ± 6.1 kg/m²) compared with the remaining 299 patients in the control group (P = .04, P = .002, respectively). There were no significant differences in other demographic and clinical characteristics between the patients with open-label amiodarone and the remaining patients in the control group.

**Figure 1** Figure reflects an updated analysis in which 66 patients with open-label amiodarone were excluded from the control group. Odds ratio (OR) and 95% confidence limits of hypothyroidism (TSH > 4.5) for all amiodarone-treated patients and each subgroup of these patients in terms of age, ischemic heart disease, diabetes, and duration of AF before the treatment compared with the control group in which the patients remained on sotalol or placebo. Overall, patients on amiodarone had a higher likelihood to develop hypothyroidism compared with those in the control group (odds ratio 4.5, 95% confidence limit 2.8-7.2). The likelihood of developing hypothyroidism in patients on amiodarone was significantly higher than that in patients who were in the control group in all predefined strata.

There was a trend toward a higher incidence of hyperthyroidism, defined as a TSH < 0.35 mU/L, in patients on amiodarone compared with those in the control group (5.3% vs 2.4%, P = .07) (Table 2). Among the 13 patients with low TSH levels in the amiodarone group, there were 8 patients with mild subclinical hyperthyroidism (TSH 0.1-0.34 mU/L), 4 patients with more significant subclinical hyperthyroidism (TSH < 0.1 mU/L), and 1 patient with overt hyperthyroidism requiring immediate treatment with methimazole.
There were 66 patients in the control group who were assigned to sotalol or placebo but treated with open-label amiodarone during follow-up. It was noted that 11 of these 66 patients developed subclinical hypothyroidism and 1 patient developed hyperthyroidism.

**Time to Elevated TSH**

Patients tended to develop hypothyroidism early in the study. Figure 2 displays the cumulative percentage of the TSH elevations that had been detected by month among the patients who developed hypothyroidism. Fifty-eight percent of patients who developed hypothyroidism in the amiodarone group and 50% in the control group were detected at the first 3 months after treatment inception. Hypothyroidism was detected in approximately 76% of the patients in the amiodarone group and 80% in the control group by 6 months. Statistical differences in rates of elevated TSH levels were not found between the amiodarone and control groups. It also was noted that 91.7% of the patients on amiodarone who developed overt TSH elevations (>10 mU/L) had been detected at 6 months and 88.7% of the milder elevations in TSH levels (4.5-10 mU/L) had been detected at the end of the first year.

**Treatment with Levothyroxine**

Patients who developed elevated TSH levels while on amiodarone were more likely to have been treated with levothyroxine than similar patients in the control group. At 6 months and 1 year, 29.7% and 52.7%, respectively, of the patients with elevated TSH levels in the amiodarone group were receiving supplemental levothyroxine. In contrast, none of the patients who developed hypothyroidism in the control group were treated with levothyroxine (P < .0001). It also was noted that among the amiodarone group a significantly higher proportion of patients with overt hypothyroidism were treated with levothyroxine than those with subclinical hypothyroidism. At 6 months, 25.0% of the patients with overt hypothyroidism in the amiodarone group used levothyroxine, compared with 4.7% of the patients with subclinical hypothyroidism in the same group (P = .002). Similarly, at 1 year, approximately 43% of patients in the amiodarone group with overt hypothyroidism were taking levothyroxine, whereas only 9.8% of the patients with subclinical hypothyroidism were prescribed levothyroxine (P < .0001).

**DISCUSSION**

Since amiodarone became available in the United States for anti-arrhythmic therapy in the 1980s, there have been numerous reports of associated changes in thyroid hormone metabolism, as well as clinically significant thyroid dysfunction. Our study shows that amiodarone-induced hypothyroidism is common among a cohort of older men treated for atrial fibrillation as compared with a control group in a blinded study. If subclinical hypothyroidism, TSH >4.5-10 mU/L, is included, 31% of the patients on amiodarone developed hypothyroidism. Although antibody testing was not done in our patients, the rate of positive antithyroid antibodies in this predominantly white male cohort is likely to be similar to the 12.9%-14.4% reported among a large population of 60-79-year-old white males in the NHANES III (National Health and Nutrition Examination Survey) study. Thus, despite a lower predisposition to thyroid dysfunction in men, nearly one third of all patients treated with amiodarone developed some degree of hypothyroidism, compared with 6.9% among the controls (P < .0001). This incidence of high TSH levels among our control group is similar to the 8%-12% reported for men and women from 60-79 years of age in the NHANES III study. Because T4 levels were not consistently obtained during the follow-up period, we cannot determine the rate of overt hypothyroidism as defined by an elevated TSH level with low FT4. Instead, TSH levels above 10 mU/L were used as the cutoff for overt hypothyroidism, and were found among 5.0% of the amiodarone-treated group, compared with 0.3% in the control group (P < .001).

Patients who developed elevations in their TSH levels did so early in both the amiodarone and control groups. At 6 months, 76% of the cases of hypothyroidism in the amiodarone group and 80% of the cases of hypothyroidism in the control group had been detected. Of the patients on amiodarone who developed TSH elevations above 10 mU/L, 92% had been detected at 6 months. A trend showed that hyperthyroidism, defined as TSH < 0.35 mU/L, was more common among the amiodarone-treated patients. Because hyperthyroidism was a subclinical entity in all but 1 patient, and rare in absolute numbers, the analysis was directed toward only the hypothyroid patients.

Amiodarone contains 37% iodine by weight. A 200-mg standard daily dose provides about 300 times the usual daily iodine intake. With initiation of treatment, the thyroid rapidly responds to the iodine load with a reduction in thyroid hormone synthesis, known as the Wolff-Chaikoff effect. Patients with normal thyroid function “escape” from the Wolff-Chaikoff effect. With normal thyroid function “escape” from the Wolff-Chaikoff effect by reducing thyroid iodide transport. Predictable changes of hormone levels that occur within the first week of therapy include a decrease in serum T3 levels and increase in serum reverse T3, T4, and TSH levels due to inhibition of type 1 5'-deiodinase in peripheral tissues and type 2 5'-deiodinase in the pituitary. After approximately 3 months of amiodarone, the compensatory increase in T4 levels reaches a steady state, and a majority of patients regain normal TSH levels. Through this escape mechanism, most patients remain clinically euthyroid while taking amiodarone. However, the large iodine load can lead to hypothyroidism in patients who do not escape from the Wolff-Chaikoff effect. Additionally, a more recent study by Tedelind et al reported that amiodarone and its iodide-free analog dronedarone are capable of inhibiting iodide uptake by thyroid follicular cells by way of an iodine-independent mechanism that does not involve the sodium-iodide symporter.
Amiodarone-induced hypothyroidism is more common among populations with sufficient iodine intake, such as in the United States. One study comparing an iodine-sufficient area of Massachusetts and an iodine-deficient area of Italy found rates of amiodarone-induced hypothyroidism, as defined by elevated TSH levels and low or low-normal thyroxine level, to be 22% in Massachusetts and 5% in Italy. Other risk factors for amiodarone-induced hypothyroidism include female sex and the presence of antithyroid antibodies. Antithyroid peroxidase antibodies are more common among white compared with black and Mexican-American individuals; 14.3%, 5.3%, and 10.9%, respectively. Among a group of 58 patients studied in the Netherlands with an overall incidence of amiodarone-induced hypothyroidism of 6.9%, female sex and antithyroid antibodies were associated with relative risks of hypothyroidism of 7.9 and 7.3, respectively. Women with antithyroid antibodies had a combined relative risk for developing amiodarone-induced hypothyroidism of 13.5. Less is known about the development of amiodarone-induced hypothyroidism in men. Albert and colleagues reported the thyroid function tests of a male-predominant group of 99 patients were treated with levothyroxine.

In summary, amiodarone-induced hypothyroidism developed in 30.8% of older men treated with amiodarone for chronic atrial fibrillation compared with the control group and presented early during therapy. Serum TSH levels >10 mU/L were found in 5.0% of amiodarone-treated men, and this should warrant treatment with thyroxine. Hyperthyroidism occurred in 5.3% of amiodarone-treated patients, but was a subclinical entity in all but 1 case and not statistically different from the rate in the control group. Given the high rate of hypothyroidism among patients taking amiodarone, monitoring of thyroid function is recommended at baseline, 3 months, and every 6 months thereafter during the therapy.

References
CLINICAL RESEARCH STUDY

Randomized Trial to Improve Fracture Prevention in Nursing Home Residents

Cathleen S. Colón-Emeric,a,b Kenneth W. Lyles,a,b Paul House,c Deborah A. Levine,d Anna P. Schenck,c Jeroan Allison,d Joel Gorospe,e Mary Fermazin,e Kristi Oliver,d Jeffrey R. Curtis,d Norman Weissman,d Aiyuan Xie,d Kenneth G. Saagd

aDuke University Center for Aging and Human Development, Durham, NC; bDurham VA Geriatric Research, Education, and Clinical Center (GRECC), Durham, NC; cCarolinas Center for Medical Excellence, Cary, NC; dCenter for Education and Research on Therapeutics (CERTs) of Musculoskeletal Disorders, University of Alabama at Birmingham, Birmingham, Ala; eHealth Services Advisory Group, Phoenix, Ariz.

ABSTRACT

BACKGROUND: Interventions to improve the fracture prevention in nursing homes are needed.

METHODS: Cluster-randomized, single-blind, controlled trial of a multi-modal quality improvement intervention. Nursing homes (n = 67) with ≥10 residents with a diagnosis of osteoporosis or recent hip fracture (n = 606) were randomized to receive an early or delayed intervention consisting of audit and feedback, educational modules, teleconferences, and academic detailing. Medical record abstraction and the Minimum Data Set were used to measure the prescription of osteoporosis therapies before and after the intervention period. Analysis was at the facility-level and Generalized Estimating Equation modeling was used to account for clustering.

RESULTS: No significant improvements were observed in any of the quality indicators. The use of osteoporosis pharmacotherapy or hip protectors improved by 8.0% in the intervention group and 0.6% in the control group, but the difference was not statistically significant (P = .72). Participation in the intervention activities was low, but completion of the educational module (odds ratio [OR] 4.8, 95% confidence interval [CI], 1.9-12.0) and direct physician contact by an academic detailer (OR 4.5, 95% CI, 1.1-18.2) were significantly associated with prescription of osteoporosis pharmacotherapy or hip protectors in multivariable models.

CONCLUSIONS: Audit-feedback and education interventions were ineffective in improving fracture prevention in the nursing home setting, although results may have been tempered by low participation in the intervention activities. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Nursing homes; Osteoporosis; Quality improvement

Fracture prevention in nursing homes is important for several reasons. With the prevalence of low bone mineral density near 90%, and a high rate of falls, the nursing home population has one of the highest fracture rates at 13 fractures/100 person-years. In addition, 60%-75% of patients with an acute hip fracture spend time in nursing facilities. This group also has an elevated risk of subsequent fractures. Clinical trials suggest that bisphosphonates are safe and effective in nursing home residents. Although few clinical practice guidelines specifically address the nursing home population, pharmacologic therapies are recommended for most hip fracture patients and selected long-term care residents at the highest risk.
Despite the importance of fracture prevention in the nursing home, previous studies have demonstrated low rates of evaluation and treatment.\textsuperscript{10-13} We reported that only one third of ambulatory nursing home residents known to have osteoporosis or recent hip fracture receive any osteoporosis pharmacologic therapy or external hip protectors.\textsuperscript{14} Moreover, there is substantial variation in the performance of nursing homes (range of 0%-85% of residents receiving therapies), suggesting that substantial improvements are possible in many facilities.\textsuperscript{14}

Changing provider behavior is, however, a challenging proposition. Studies in other settings have identified interventions that are sometimes effective,\textsuperscript{15} such as contact with opinion leaders, audit and feedback,\textsuperscript{16} faxed reminders,\textsuperscript{17} and educational materials to providers and patients.\textsuperscript{18,19} Little is known about which interventions are effective in the nursing home.

We developed a multi-modal intervention to improve fracture prevention in residents with documented osteoporosis or recent fracture.

**CLINICAL SIGNIFICANCE**

- In nursing homes, many patients at high risk of fracture do not receive the fracture prevention therapies (bisphosphonates and hip protectors) indicated by clinical practice guidelines.
- In a study of 67 nursing homes, quality-improvement interventions (audit and feedback, educational modules, teleconferences, and academic detailing) only slightly (and nonsignificantly) improved adherence to anti-fracture practice guidelines.
- Systematic interventions that remove barriers to providing preventive care are needed.

**METHODS**

This analysis combines data from studies completed with the Quality Improvement Organizations in Arizona and North Carolina. The studies were approved by the Duke University and University of Alabama at Birmingham Institutional Review Boards. The Clinical Trial Registry number is NCT00280943 (http://www.clinicaltrials.gov).

**Facility Selection and Randomization**

The Minimum Data Set, a database of clinical and demographic information collected quarterly on all Medicare and Medicaid eligible residents, was used to identify nursing homes in North Carolina and Arizona, with at least 10 residents diagnosed with osteoporosis or a hip fracture within 180 days. Administrators from 67 of 249 eligible nursing homes agreed to enroll. The nursing homes were randomized within each state to receive the study intervention immediately (intervention group) or after the follow-up chart abstraction was completed (control group) using a random number generator.

**Resident Selection**

Residents aged 50 years or older with either a history of hip fracture or a diagnosis of osteoporosis during a 6-month time period were identified. Residents had to be ambulatory or transfer independently, and have a length of stay of at least 4 weeks. In order to obtain a sample of residents most likely to be candidates for the full range of fracture prevention therapies, we excluded residents with active cancer, severe dementia, end-stage renal disease, extensive assistance in physical functioning, hospice care, or estimated life expectancy \(\leq 6\) months. Although fracture prevention may be warranted in many of the excluded residents, including them in our sample would lead to lower rates of response to the intervention because some residents would be deemed unlikely to benefit from most of the therapies.

**Intervention**

Nursing home staff in the intervention group received: continuing educational modules on osteoporosis evaluation and treatment; audit and feedback; academic detailing from osteoporosis opinion leaders; case-based teleconference on osteoporosis quality improvement; and an osteoporosis toolkit. Control nursing homes had no further contact until after the study was complete, at which time they received a similar intervention.

The intervention period began January 3, 2005 and it ended May 13, 2005 in Arizona and July 1, 2005 in North Carolina.

Two case-based educational modules for medical staff and nursing staff were developed and pilot-tested based on recommendations from focus groups.\textsuperscript{20} The modules could be completed over the Internet or on paper in less than 1 hour, and 1-hour CME/CEU (continuing medical education/continuing education unit) credit was provided. Recommendations in the modules were based on osteoporosis clinical practice guidelines\textsuperscript{7} and focused on secondary fracture prevention, including assessment for vitamin D deficiency; calcium and vitamin D supplementation; osteoporosis pharmacotherapy; hip protectors; and fall prevention. The director of nursing and all medical providers received at least 3 fax, e-mail, and telephone reminders to complete the modules.

Audit and feedback was provided on weeks 3, 8, and 18 to all administrators in the intervention group. The blinded report included graphics that compared their facility with other study facilities in the state (Figure). Because of privacy concerns, we did not supply the audit and feedback report to medical providers, but asked the administrator to do so.

Academic detailing to all medical providers was completed by osteoporosis opinion leaders. At least 3 attempts were made to reach each medical provider directly by telephone, and if unsuccessful, messages about the study were left.
Teleconferences were offered 4 times throughout the intervention period. Nursing staff and medical staff were invited to a case-based presentation on osteoporosis quality improvement via a faxed and mailed letter. One teleconference was audiotaped, and a compact disc sent to all medical providers.

Finally, a “toolkit” of materials was provided to each administrator. This included posters to hang in the facility and resident/family brochures. Fall prevention tools and links to osteoporosis clinical practice guidelines and patient information were provided on the module website.

Data Collection

Based on guideline recommendations, quality indicators for osteoporosis evaluation and fracture prevention were measured. The primary outcome variable was prescription of osteoporosis pharmacotherapy or hip protectors. We also measured a combined outcome variable of prescription of osteoporosis pharmacotherapy or hip protectors or calcium and vitamin D supplements. We included measures with and without calcium and vitamin D supplements because many practice guidelines do not recommend them as monotherapy for secondary fracture prevention, and because high baseline prescription rates might introduce a ceiling effect. Total daily dose of calcium and vitamin D were not assessed because they could come from multiple sources and were difficult to abstract reliably. Facility fracture rates were an exploratory outcome measure.

Trained data collectors, blinded to intervention status, abstracted data from the medical record before and after the intervention. Data collectors reviewed prescriptions in a 6-month time period beginning at the first time a fracture or osteoporosis diagnosis was recorded in the Minimum Data Set. The entire medical record was reviewed for selected comorbidities, bone mineral density, and laboratory testing. A random 10% of charts was re-abstracted by a second data collector, and inter-rater reliability was maintained at >90%.

Facility characteristics were obtained from public use datasets (http://www.medicare.gov/NHCompare). Some resident characteristics were obtained from the Minimum Data Set.

Analysis

Data were analyzed at the facility level. Nursing homes in Arizona and North Carolina were combined for the main analysis. The change in the proportion of residents receiving therapy between the pre- and postintervention periods was compared between the intervention and control nursing homes using t tests. All randomized facilities were analyzed regardless of their participation in the study. In order to adjust for characteristics that might impact prescription of osteoporosis therapies, multivariable logistic regression models with generalized estimating equation adjustment for repeated binary outcomes were constructed with backwards selection, using all variables with a baseline univariate $P < .20$ and variables with high clinical significance (age, race, state). The intervention time period by group interaction term was tested using chi-squared as a test of the impact of the intervention on prescription of therapies. This method accounted for the complex nesting of residents within providers and nursing facilities.

A prespecified exploratory analysis compared fracture rates in the intervention period between intervention and control facilities using $t$ test. In order to examine the impact of participation in the intervention components, we constructed Generalized Estimating Equation models using backwards selection, with covariates significant at the $=.20$ level and the intervention participation variables.

Sample Size Considerations

Originally, we calculated that enrolling 128 nursing homes would provide 80% power to detect a 10% difference in the change in prescription of any fracture protection between the 2 arms. However, recruitment was challenging, and 67 nursing homes were ultimately enrolled. Post hoc, we determined that our sample size provided 80% power to detect a 17% difference, and 98% power to detect a 20% difference in the change in proportion of residents receiving any fracture protection in the intervention facilities compared with the control facilities.

RESULTS

Baseline characteristics of the 67 nursing homes and 606 residents are shown in Table 1. Intervention residents were more likely to be African American, younger, and use tobacco; and less likely to have previous fracture or dysphagia.

The use of fracture prevention strategies in the preintervention and postintervention periods is shown in Table 2. The primary endpoint of osteoporosis pharmacotherapy or hip protectors improved in intervention homes from 32.6% to 40.6% (difference 8.0%) and remained unchanged in control homes from 38.6% to 39.2%, (difference 0.6%), but the differences were not statistically significant ($P = .72$).
The combined endpoint of osteoporosis pharmacotherapy or hip protectors, or calcium and vitamin D supplements showed a 7% improvement in both intervention and control homes, but baseline treatment rates exceeded 70%, suggesting a possible ceiling effect. Nonsignificant trends toward greater improvement in intervention versus control homes.

### Table 1: Characteristics of the Intervention and Control Nursing Homes and Target Residents during the Control Period

<table>
<thead>
<tr>
<th>Facility characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>For profit (%)</td>
<td>75.8</td>
<td>82.4</td>
<td>.22</td>
</tr>
<tr>
<td>Total number of residents (mean)</td>
<td>110.3</td>
<td>109.3</td>
<td>.62</td>
</tr>
<tr>
<td>Rural location (%)</td>
<td>18.8</td>
<td>18.5</td>
<td>.93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resident characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (%)</td>
<td>85.0</td>
<td>87.2</td>
<td>.43</td>
</tr>
<tr>
<td>Race/ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>81.9</td>
<td>80.8</td>
<td>.73</td>
</tr>
<tr>
<td>African American</td>
<td>5.5</td>
<td>2.2</td>
<td>.04</td>
</tr>
<tr>
<td>Other</td>
<td>12.6</td>
<td>16.9</td>
<td>.14</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>83.0</td>
<td>85.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

| Insurance status (%)     |              |         |          |
| Medicare                 | 30.4         | 34.5    | .28      |
| Medicaid                 | 17.0         | 13.1    | .17      |
| Private                  | 8.5          | 8.3     | .92      |
| Other                    | 79.9         | 75.7    | .22      |

| Previous fracture (%)    | 16.7         | 24.6    | .02      |
| Resident ambulatory (%)  | 55.6         | 62.0    | .11      |
| Falls in last 90 days (%)| 33.8         | 37.4    | .36      |
| Cognitive impairment (%) | 43.3         | 46.0    | .51      |
| Gastroesophageal reflux (%) | 39.0     | 43.8    | .23      |
| Ulcer disease or esophagitis (%) | 7.5 | 10.5 | .19 |
| Breast cancer (females only) (%) | 2.7 | 4.5 | .25 |
| Dysphagia (%)            | 14.7         | 20.8    | .05      |
| Thromboembolic disease (%) | 8.5        | 8.3     | .92      |
| Tobacco use (%)          | 24.6         | 16.6    | .015     |
| Alcohol abuse (%)        | 5.1          | 3.8     | .44      |

### Table 2: Proportion of Residents with Osteoporosis or Recent Hip Fracture Receiving Fracture Prevention Interventions Before and After the Intervention Period in the Intervention and Control Homes

<table>
<thead>
<tr>
<th>Diagnostic testing modalities</th>
<th>Before Intervention (n = 33)</th>
<th>After Intervention (n = 33)</th>
<th>Control (n = 34)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone mineral density measurement (%)</td>
<td>1.2</td>
<td>0.3</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Serum calcium level</td>
<td>58.0</td>
<td>77.5</td>
<td>61.2</td>
<td>73.8</td>
</tr>
<tr>
<td>25(OH) vitamin D level (%)</td>
<td>0.3</td>
<td>0.5</td>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fracture prevention modalities</th>
<th>Before Intervention (n = 33)</th>
<th>After Intervention (n = 33)</th>
<th>Control (n = 34)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (%)</td>
<td>72.5</td>
<td>82.8</td>
<td>66.0</td>
<td>74.5</td>
</tr>
<tr>
<td>Vitamin D (%)</td>
<td>68.7</td>
<td>76.3</td>
<td>57.1*</td>
<td>70.5</td>
</tr>
<tr>
<td>Bisphosphonate (%)</td>
<td>17.9</td>
<td>25.8</td>
<td>20.2</td>
<td>20.6</td>
</tr>
<tr>
<td>Calcitonin (%)</td>
<td>11.5</td>
<td>15.6</td>
<td>17.3</td>
<td>16.5</td>
</tr>
<tr>
<td>Raloxifene (%)</td>
<td>2.7</td>
<td>2.8</td>
<td>3.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Teriparatide (%)</td>
<td>0.3</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HRT in women (%)</td>
<td>2.3</td>
<td>2.4</td>
<td>3.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Testosterone in men (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hip Protectors (%)</td>
<td>2.8</td>
<td>3.4</td>
<td>1.3</td>
<td>7</td>
</tr>
<tr>
<td>Osteoporosis pharmacotherapy or hip protectors (%)</td>
<td>32.6</td>
<td>40.6</td>
<td>38.6</td>
<td>39.2</td>
</tr>
<tr>
<td>Osteoporosis pharmacotherapy or hip protectors or calcium and vitamin D (%)</td>
<td>79.0</td>
<td>80.1</td>
<td>72.8</td>
<td>86.8</td>
</tr>
</tbody>
</table>

HRT = hormone replacement therapy.

*Indicates P < .05 for intervention vs control in the specified time period.
were seen for most other indicators. There were no significant differences in performance on the quality measures between the states.

Multivariable models testing the impact of the intervention on the primary and combined outcome measures were not statistically significant (odds ratio [OR] 1.0, 95% confidence interval [CI], 0.9-1.2, \( P = .18 \)) even after adjusting for baseline factors that were imbalanced, including bed size, age, race, sex, previous fracture, insurance status, ambulatory status, gastrointestinal reflux, breast and endometrial cancer, dysphagia, and tobacco use. Incident fracture rates during the 6-month intervention period were similar between intervention (4.3%) and control facilities (4.1%), and were unchanged from the preintervention period. Fall rates were unchanged in the pre- and postintervention periods at 50%-51%.

Among the intervention facilities, participation in intervention activities was generally low except for audit feedback, which was provided to 100% of homes (Table 3). Intervention homes with at least 1 participant in the nursing educational module tended toward greater improvement in prescription of osteoporosis pharmacotherapy or hip protectors (19.5%) than either control homes (0.6%) or intervention homes without a nursing educational module participant (6.4%, \( P = .36 \)). Participation in the medical provider educational module showed a similar pattern. In a multivariable Generalized Estimating Equation model including all covariates used above and participation variables, direct physician contact with the academic detailer (OR 4.5, 95% CI, 1.1-18.2, \( P = .03 \)) and physician completion of the CME module (OR 4.8, 95% CI, 1.9-12.0, \( P = .001 \)) were significantly associated with prescription of osteoporosis pharmacotherapy or hip protectors compared with control nursing homes and intervention homes without participation. No significant associations were observed when calcium and vitamin D supplements were added to the primary outcome measure, although treatment rates in the follow-up period exceeded 80% for all groups, again suggesting a ceiling effect.

**DISCUSSION**

We demonstrated a small, nonsignificant improvement in the prescription of fracture prevention therapies after the implementation of a quality improvement intervention. Although our study cohort had high fracture risk given their fall rate (35% fell within 90 days) and previous fracture history (20%), prescription of fracture prevention therapies other than calcium and vitamin D remained low. The magnitude of provider behavior change is consistent with that found in similar osteoporosis quality improvement studies in other settings, but is likely insufficient to have an impact on fracture rates.

This study has several strengths. The multi-modal intervention included multiple proven techniques. We targeted not only medical providers, but also the nursing staff and administrator, who have considerable influence on decision-

### Table 3

<table>
<thead>
<tr>
<th>Activity</th>
<th>Control</th>
<th>Intervention Homes with Engagement in Activity</th>
<th>Intervention Homes with No Engagement in Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audit feedback</td>
<td>34</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Homes with academic detailer speaking directly to at least 1 physician</td>
<td>6.4</td>
<td>6.4</td>
<td>6.4</td>
</tr>
<tr>
<td>CME module completed by at least 1:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing staff</td>
<td>34</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Medical staff</td>
<td>34</td>
<td>6.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Teleconference participation by at least 1 staff</td>
<td>34</td>
<td>26</td>
<td>21</td>
</tr>
</tbody>
</table>

No statistically significant differences in the 2 intervention subgroups compared with the control group.

* Because all intervention homes received audit and feedback, the cell is not applicable.
making. The study was randomized, outcomes assessment blinded, and powered to detect a clinically meaningful difference. Regulations for documentation in nursing homes make it unlikely that medication therapies were not recorded in the medical record. We included only residents with clear indications for osteoporosis therapy and the fewest comorbidities that would limit the applicability of clinical practice guidelines in the nursing home setting. Despite these strengths, there are several potential explanations for the lack of effect.

First, we had difficulty engaging nursing homes and providers in our study. Although previous research has shown that a large majority of Medical Directors and Directors of Nursing believe that fracture prevention is important and effective, we successfully recruited only about half of the number of facilities we had anticipated. Administrators most often cited staff turnover, regulatory survey demands, and competing clinical projects as reasons for not participating in the study. As a result, our final number of nursing homes allowed sufficient power to detect a 17% or greater improvement. After enrollment, few providers participated in the elements of our intervention despite repeated encouragement. The issues of engagement and timing have been shown to be important in behavior change interventions. It is clear that engagement was critical in this study, because those providers we successfully engaged were more likely to improve their osteoporosis management compared with those who did not participate. Providers who engaged in the intervention are likely to be more motivated, knowledgeable, and willing to change. This may partly explain the association between participation and improvement in our study. Previous studies have suggested that interventions work best when the timing of the intervention is soon after the triggering event; in our study, an intervention occurring sooner after a fracture may have been more effective in assisting providers to change their behavior. An important goal in future research is to either identify ways to engage a broader range of providers, or to use systems that do not require individual physician practice change to improve quality.

Second, there may be barriers to fracture prevention in the nursing home environment that were not sufficiently addressed by our intervention. In a survey of more than 1000 medical directors and directors of nursing, reimbursement issues, short length of stay, and regulatory oversight about the number of medications prescribed were endorsed as the primary barriers to adhering to osteoporosis practice guidelines. For example, a nursing home receiving a capped reimbursement for the rehabilitation of a hip fracture patient has little incentive to add an expensive osteoporosis medication during their stay. Bone density scans are logistically difficult to obtain for frail residents, and Medicare reimburses for testing only every 2 years. These factors cannot be easily addressed by an intervention such as ours, and may require systems and health care policy change so that the goals of residents, administrators, and practitioners are better aligned.

Third, the osteoporosis guideline recommendations themselves may not be optimally suited for the frail nursing home population. Applying guideline recommendations to residents with competing comorbidities, surrogate decision-makers, and varying goals of care is challenging; for example, nearly 25% of our sample had peptic ulcer disease, esophagitis, or dysphagia that would preclude use of oral bisphosphonates (Table 1). Most fracture prevention studies included postmenopausal women, and generalization to frail older populations also is problematic, although previous surveys have shown that a large majority of nursing home medical directors believe that osteoporosis guidelines are relevant to their patients. Guidelines specific to the nursing home population that assist providers in determining residents most likely to benefit are needed.

There have been relatively few published randomized trials of quality improvement initiatives in the nursing home to compare with our results. Effective interventions generally require on-site personnel or extensive provider involvement in intervention development. Other studies have shown a limited effect of group training sessions such as Quality Improvement Collaboratives and highlighted the lack of effective quality improvement infrastructure in nursing homes. To circumvent some of these issues, systematic interventions that remove the responsibility for providing preventive care from individual practitioners are needed. Examples of such interventions might include standing orders for osteoporosis care that are implemented routinely unless a provider or patient “opts out,” or automated telephone reminders or letters to patients and families on discharge from the hospital after a fracture.

Fracture prevention remains challenging in the nursing home setting. Further studies are needed to identify effective means of changing clinicians’ behavior and testing system-wide interventions that could prove more effective than traditional quality improvement approaches.

References


Impact of a Fluoroquinolone Restriction Policy in an Elderly Population

Muhammad Mamdani, PharmD, MA, MPH,a,b,c David McNeely, MD,c,e Gerald Evans, MD,g Janet Hux, MD, SM,a,c,d Paul Oh, MD,c,f Natalie Forde, MSc,a John Conly, MDh

aThe Institute for Clinical Evaluative Sciences; University of Toronto Faculties of bPharmacy and cMedicine; dSunnybrook and Women’s College Health Sciences Centre, Toronto Western Hospital, Toronto, Ontario; eUniversity Health Network and fToronto Rehabilitation Institute, Toronto, Ontario; gQueen’s University Faculty of Health Sciences and Kingston General Hospital, Kingston, Ontario; hUniversity of Calgary Faculty of Medicine and Foothills Medical Centre, Calgary, Alberta.

ABSTRACT

BACKGROUND: In light of growing concerns of bacterial resistance to fluoroquinolones, the province of Ontario instituted a fluoroquinolone restriction policy in March of 2001. The objective of this study was to examine the immediate impact of this policy on the rates of antibiotic prescription use and infectious disease-related hospitalizations among elderly individuals who are dispensed antibiotics.

METHODS: An interrupted time series analysis was conducted from January 1, 1994, to March 31, 2002, using administrative health care databases covering more than 1.4 million residents of Ontario, Canada, aged 65 years and older. Population rates of antibiotic use and infectious disease-related hospitalizations within 4 weeks after an antibiotic prescription were examined using interventional autoregressive integrated moving average models.

RESULTS: Immediately after the introduction of the fluoroquinolone policy, fluoroquinolone prescription rates decreased to approximately 70% of expected rates (P < .01). Approximately 30% higher than expected use of sulfonamide (P = .01) and urinary anti-infectives (primarily nitrofurantoin and trimethoprim; P < .01) were observed within 1 year after policy implementation. No significant changes in the use of any other groups of antibiotics were observed. Although no significant changes in the rates of overall infection-related hospital admissions among antibiotic users were observed, the rate of hospital admission for gastrointestinal infections was 32% lower than expected in the 1 year after the policy change (P < .01). The hospital admission rate for urinary tract infections was approximately 8% higher than expected (P < .01).

CONCLUSIONS: These findings suggest that formulary restrictions to fluoroquinolones can be implemented effectively to decrease use among an elderly population without adverse impact on hospital admission rates. © 2007 Elsevier Inc. All rights reserved.
fluoroquinolone use, such as academic detailing,\textsuperscript{9} formulary restriction,\textsuperscript{10-13} and multidimensional interventions.\textsuperscript{14}

In the year 2000, Ontario’s Drug Quality and Therapeutics Committee (DQTC) undertook a review of antibiotics on the Ontario Drug Benefits (ODB) Formulary and recommended criteria to limit the prescribing of fluoroquinolones based on concerns of growing antibiotic resistance and misuse. The Ontario DQTC review of antibiotics noted a particular concern of growing quinolone resistance to Acinetobacter species, Pseudomonas aeruginosa, S. pneumoniae, Staphylococcus aureus, Neisseria gonorrhoea, Campylobacter jejuni, Salmonella typhimurium DT104, and extended spectrum β-lactamase-producing strains of Escherichia coli and Klebsiella pneumoniae. The DQTC provides an essential advisory service to the Ontario government through the assessment of drug products for government funding and consists of practicing physicians and pharmacists who have expertise in a wide range of specialties, including geriatrics, infectious disease, pharmacology, health economics, epidemiology, and other disciplines. The DQTC mandate also includes the ongoing monitoring and evaluation of drug product reimbursement under the ODB program.

Although previous studies have demonstrated that formulary restriction is an effective means of controlling drug use,\textsuperscript{10-13} concerns have been raised regarding the clinical consequences of such measures.\textsuperscript{12} For example, a retrospective study has suggested that a restrictive formulary policy for fluoroquinolones may result in increased population rates of hospitalization for pyelonephritis and bronchitis.\textsuperscript{12} We conducted a population-based study to examine the impact of Ontario’s formulary restriction policy for fluoroquinolones on the rates of overall antibiotic prescription use and infectious disease-related hospitalizations among those dispensed antibiotics.

**METHODS**

**Study Design**

We conducted a population-based cross-sectional time series analysis from January 1, 1994, to March 31, 2002, using administrative health care databases covering the entire population of 1.4 million residents of Ontario, Canada, aged 65 years and older. This time period was divided into 33 quarterly intervals. Ontario’s elderly population has universal access to prescription drugs, hospital care, and physician services. This research study was approved by the Ethics Review Board of Sunnybrook and Women’s College Health Sciences Centre (Toronto, Ontario, Canada).

**Data Sources**

The administrative health care databases in Ontario allowed for the assessment of the prevalence of prescription drug use and hospitalizations. The databases included computerized pharmacy records of the ODB program, which records prescription drugs reimbursed by the public drug program for all Ontario residents 65 years of age and older. Before March 1, 2001, all antibiotics were listed as General Benefit drugs and were not subject to any formulary restrictions. As of March 1, 2001, however, restrictions were imposed on all fluoroquinolones, except norfloxacin, making them “Limited Use” drugs whose prescription required that prescribers indicate the reason for use on a special prescription pad. These policy changes are highlighted in Table 1.

We obtained hospitalization records for all residents of Ontario 65 years of age and older from the Canadian Institute for Heath Information Discharge Abstract Database, which contains a detailed record of all hospital admissions, including diagnostic information. The Ontario Registered Persons Database contained basic demographic and vital statistics information for each Ontario resident. Each of these databases bears a unique patient identifier that facilitates deterministic linkage. The databases used in this study have been shown to be of high quality\textsuperscript{15} and are often used for research purposes.

**End Point Ascertainment**

Quarterly temporal trends for 2 end points were assessed: antibiotic prescription use rates and hospital admission rates for infectious disease-related admissions among those dispensed antibiotics. The rate of antibiotic prescription use in each time interval was determined by dividing the total number of antibiotic prescriptions dispensed by the total number of individuals alive at the beginning of the interval. Antibiotic prescription use rates were expressed as the number of prescriptions per 1000 persons per quarterly interval. The rates of hospitalization for infectious disease among those dispensed an antibiotic were estimated in each interval by dividing the number of infectious disease-related hospitalizations within 4 weeks after the dispensing of an outpatient antibiotic prescription by the total number of individuals dispensed an antibiotic in that interval. Only those
admitted to a hospital with a most responsible diagnosis of an infectious disease were included for analysis. Transfer admissions were excluded to avoid double-counting. Consistent hospitalization data were available until March 31, 2002, and analyses examining hospitalization rates were therefore limited to this time interval. Diagnoses were captured in the administrative databases using the International Classification of Diseases, revision 9 (ICD-9) coding system until March 31, 2002. Hospital diagnoses were subsequently coded using an ICD-10 coding system. The translation of coding between the ICD-9 and ICD-10 systems is not congruent, and therefore analyses were limited to aforementioned time frames. Hospitalization rates were expressed as the number of events per 100,000 persons per quarterly interval. All hospital admissions assessed were required to have a most responsible diagnosis of a relevant infectious disease. Hospital admission for infectious disease was categorized into 8 broad groupings: gastrointestinal infections, intra-abdominal infections, urinary tract infections, upper respiratory tract infections, pulmonary infections, cellulitis/skin and soft tissue infections (with or without abscess), unclassified bacterial infections, and miscellaneous infections (sexually transmitted diseases, central nervous system infections, dentoalveolar infections, osteomyelitis).

### Table 1  Ontario Drug Benefits Restrictions Imposed on Fluoroquinolone Use as of March 7, 2001

<table>
<thead>
<tr>
<th>Drug</th>
<th>Listing Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Limited use for the treatment of patients with:</td>
</tr>
<tr>
<td></td>
<td>SST/BJ (gram-negative bacteria): SST/BJ resulting from gram-negative bacteria;</td>
</tr>
<tr>
<td></td>
<td>severe diabetic foot infection; severe otitis externa; decubitus ulcers</td>
</tr>
<tr>
<td></td>
<td>GU tract: urinary tract infection/prostatitis/epididymitis caused by Pseudomonas;</td>
</tr>
<tr>
<td></td>
<td>sexually transmitted diseases</td>
</tr>
<tr>
<td></td>
<td>COPD with risk: acute bacterial exacerbation of COPD with risk factors; bronchiectasis;</td>
</tr>
<tr>
<td></td>
<td>pneumonia with risk factors; bronchiectasis; pneumonia illness with cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>GI: traveler’s diarrhea; enteric fever syndromes</td>
</tr>
<tr>
<td></td>
<td>Step-down: step-down therapy after parenteral therapy or hospital/emergency department discharge (eg, febrile neutropenia)</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>Exceptional cases of allergy or intolerance to all other appropriate therapies</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Limited use for the treatment of patients with:</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>CAP with comorbidity: CAP with comorbid illnesses or failure to first-line therapy</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Limited use for the treatment of patients with:</td>
</tr>
<tr>
<td></td>
<td>SST/BJ (gram-negative bacteria): SST/BJ infection resulting from gram-negative bacteria; severe diabetic foot infection</td>
</tr>
<tr>
<td></td>
<td>GU tract: urinary tract infection/prostatitis/epididymitis; sexually transmitted diseases</td>
</tr>
<tr>
<td></td>
<td>COPD with risk: Acute bacterial exacerbation of COPD with risk factors; bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>GI: traveler’s diarrhea; enteric fever syndromes</td>
</tr>
<tr>
<td></td>
<td>Step-down: step-down therapy after parenteral therapy or hospital/emergency department discharge (eg, febrile neutropenia)</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Exceptional cases of allergy or intolerance to all other appropriate therapies</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>General benefit</td>
</tr>
</tbody>
</table>

GU = genitourinary; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; SST = skin and soft tissue; BJ = bones and joints; CAP = community-acquired pneumonia.

### Primary and Secondary Analyses

The primary analysis examined the temporal changes in the use of fluoroquinolones and overall hospital admission rates for the infectious disease categories after the introduction of the revised ODB fluoroquinolone coverage policy. Secondary analyses examined temporal changes in each broad classification of antibiotics as outlined in Table 2, in the total antibiotic prescription use rate, and in each of the 8 categories of infectious disease-related hospitalizations after the introduction of the revised ODB fluoroquinolone coverage policy. We also examined hospitalization rates regardless of reason for admission and mortality within the 4 weeks after antibiotic prescription.

### Statistical Analysis

To examine changes in the prevalence and rates of antibiotic use and hospitalizations over time, we used time series analysis. Time series analysis,\(^1\) a collection of techniques for modeling autocorrelation in temporally sequenced data, was conducted using exponential smoothing models and interventional autoregressive integrated moving average models to model interval data from January 1994 to March 2002. Interventional autoregressive integrated moving average models incorporated a ramp function to estimate the impact of the fluoroquinolone policy on antibiotic use and
hospital admission rates. Model-derived projections and their 95% confidence intervals for the quarterly intervals from April 2001 to March 2002 were compared with actual use estimates. Stationarity was assessed using the autocorrelation function and the augmented Dickey-Fuller test.17 The autocorrelation, partial autocorrelation, and inverse autocorrelation functions were assessed for model parameter appropriateness and seasonality. The presence of white noise was assessed by examining the autocorrelations at various lags using the Ljung-Box chi-square statistic.18

RESULTS
Antibiotic use varied by season, with peak use during the first quarter of each year (ie, January to March) and lowest use during the third quarter of each year (ie, July to September). The prevalence ranged from a high of 21.6% of the elderly population (n = 283,653) during the first quarter of 1995 to a low of 14.1% of the elderly population (n = 210,196) during the third quarter of 2001. The average population per time interval was approximately 1.40 million elderly persons (standard deviation = 0.07 million), and the average number of antibiotic users per time interval was 246,559 elderly persons (standard deviation = 22,984).

Primary Analyses
Before the introduction of the fluoroquinolone policy, fluoroquinolones were the most commonly used group of antibiotics in Ontario at 63.6 prescriptions per 1000 elderly residents per quarter, followed by penicillins (60.0 prescriptions per 1000 elderly residents per quarter), macrolides (47.9 prescriptions per 1000 elderly residents per quarter), and cephalosporins (34.3 prescriptions per 1000 elderly residents per quarter). Immediately after the introduction of the fluoroquinolone policy, fluoroquinolone prescription rates decreased significantly to approximately 70% of expected rates (P < .01; Figure 1). However, within 1 year

<table>
<thead>
<tr>
<th>Table 2 Antibiotic Groupings for Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class of Antibiotic</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Quinolones</td>
</tr>
<tr>
<td>Urinary Anti-infectives</td>
</tr>
<tr>
<td>Sulfonamides and</td>
</tr>
<tr>
<td>combinations</td>
</tr>
<tr>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Macrolides</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Penicillins</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
</tbody>
</table>

Figure 1 Overall fluoroquinolone prescription utilization and hospital admission rates for infectious diseases among antibiotic users over time: quarterly rates.
after policy implementation, fluoroquinolone prescription use rates started increasing again, but the changes were not significant. Hospitalization rates for infection-related admissions among antibiotic users before the fluoroquinolone policy averaged approximately 1313 (standard deviation = 135) admissions per 100,000 elderly antibiotic users, ranging from a high of 1629 per 100,000 elderly antibiotic users during the first quarter of 1998 to a minimum of 1112 during the second quarter of 1994. No consistent significant changes in overall hospital admission rates for infection-related conditions were observed within 1 year after policy implementation \( (P = .55; \text{ Figure 1}) \).

**Secondary Analyses**

**Fluoroquinolone Antibiotic Use.** Significant changes in the use of specific fluoroquinolones were observed after policy implementation. Although ciprofloxacin use rates decreased significantly in the months after policy implementation to approximately 40% of expected use rates (actual use = 17.1 prescriptions per 1000 elderly persons per quarter vs predicted use = 43.6 prescriptions per 1000 elderly persons per quarter; \( P < .01; \text{ Figure 2} \)) and remained significantly lower than expected rates throughout the 1-year follow-up period, ciprofloxacin remained the most widely used fluoroquinolone. Significant increases in norfloxacin use also were observed after policy implementation to rates of approximately 65% higher than expected use \( (P < .01; \text{ Figure 2}) \). A significant reduction in ofloxacin prescription rates also was observed \( (P < .01) \), but this effect might be of minimal consequence given the low absolute use rates. Changes in levofloxacin, moxifloxacin, and gatifloxacin could not be estimated given the short period of time available since their introduction, although their use contributed to the increasing total fluoroquinolone use rates over time.

**Non-Fluoroquinolone Antibiotics.** No significant changes in cephalosporin \( (P = .19; \text{ Figure 3}) \), macrolide \( (P = .16) \), penicillin \( (P = .16) \), tetracycline \( (P = .52) \), or miscellaneous \( (P = .79) \) antibiotic use rates were observed. Among the

![Figure 2](image_url)  
Fluoroquinolone prescription utilization rate over time: individual fluoroquinolones.

![Figure 3](image_url)  
Non-fluoroquinolone antibiotic utilization over time: quarterly rates.
“other” antibiotics category, significant increases in the use of sulfonamide \((P = .01)\) and urinary anti-infectives (primarily nitrofurantoin and trimethoprim; \(P < .01\)) after policy implementation were observed. Observed rates were approximately 30% higher than expected for each of these groups of antibiotics by the end of the 1-year follow-up period.

**Total Antibiotic Use.** No significant changes in overall antibiotic prescription rates were observed after policy implementation \((P = .30)\).

**Infection-Related Hospitalizations.** The most common types of infection-related hospital admissions were pulmonary infections \((\sim 760\) admissions per 100,000 antibiotic users per quarter), urinary tract infections \((\sim 153\) admissions per 100,000 antibiotic users per quarter), and intra-abdominal infections \((\sim 124\) admissions per 100,000 antibiotic users per quarter). Although no significant changes in rates of overall infection-related hospital admissions among antibiotic users were observed, a significant reduction in the rate of hospital admission for gastrointestinal infections was observed \((P < .01; \text{Figure 4a})\). In the year after policy implementation, the hospital admission rate for gastrointestinal infections was approximately 32% lower than expected rates, which translates to approximately 74 fewer hospital admissions for gastrointestinal infections per 100,000 antibiotic users. However, an increase in hospital admission for urinary tract infection also was observed \((P < .01; \text{Figure 4b})\). In the year after policy implementation, the hospital admission rate for urinary tract infections was approximately 8% higher than expected rates, which translates to approximately 63 more hospital admissions for urinary infections per 100,000 antibiotic users. No significant changes in hospital admission rates for pneumonia \((P = .55; \text{Figure 4c})\), intra-abdominal \((P = .92)\), cellulitis \((P = .63)\), upper respiratory tract \((P = .96)\), unclassified bacterial \((P = .11)\), and miscellaneous \((P = .82)\) infections were observed.

**All-Cause Hospitalization and Mortality.** No significant differences in all-cause hospitalization \((P = .55)\) or mortality \((P = .62)\) rates were observed as a function of the antibiotic restriction policy.

**DISCUSSION**

A significant reduction in fluoroquinolone use after the introduction of a formulary restriction policy aimed at all fluoroquinolones (except norfloxacin) was observed in a population 65 years and older. These reductions were accompanied by increases in the use of norfloxacin, urinary anti-infectives, and sulfonamide and combination antibiotics without any significant increases in macrolide or cephalosporin use in the 1-year after policy implementation. This is an important observation given that some predicted a reciprocal increase in other classes of antimicrobials within this population, especially for respiratory tract infections. Among users of antibiotics in the population studied, a slight increase in the rate of hospital admission for urinary tract infections was associated with the policy implementation along with a significant reduction in the rate of hospital admission for gastrointestinal infections.

Given the broad spectrum of activity of fluoroquinolone antibiotics, they effectively treat both complicated and uncomplicated urinary tract infections. Fears of increased rates of complicated urinary tract infections with the restriction of fluoroquinolones have been raised because agents with a more limited spectrum of activity would need to be used in their place. Although fluoroquinolones have not traditionally been associated with gastrointestinal infections, several case-control studies have found significantly increased risks of *Clostridium difficile* infection with fluoroquinolone use, particularly the newer broad-spectrum fluoroquinolones. Many of the recently described outbreaks have been associated with elderly or nursing home populations and a study from a Canadian center suggested the pattern of the infection is changing with an increase of the proportion of cases with severe and fatal complications. Another recent Canadian study from Quebec found that the use of the newer broad-spectrum fluoroquinolones (moxifloxacin and gatifloxacin), in addition to ciprofloxacin, may have promoted a major outbreak of severe *C. difficile* infection in a predominantly elderly population that was associated with significant morbidity and mortality. The predominant strain of *C. difficile* associated with this outbreak was a single toxigenic clone that was highly resistant to fluoroquinolones. Although we were not able to extract data on *C. difficile* infections, it is interesting to speculate whether the findings of significantly fewer gastrointestinal infections is that less fluoroquinolone use in this elderly population may have been associated with less *C. difficile* infection, to which the elderly population is particularly susceptible. We acknowledge that further studies to test this hypothesis are necessary.

Several limitations of this study should be noted. First, we used administrative databases to identify and define exposure to study drugs and clinical outcomes. We have no direct measure of adherence or appropriateness of use. Because antibiotics may be used in varying doses in different regimens, the dose equivalence of various antibiotics could not be adequately examined with these data. Instead, antibiotics were examined as they are naturally used under a “real world” context in this population. Second, accurate data on antibiotic resistance could not be reported given the short follow-up of the study. Third, the generalizability of our findings to younger patients or settings with different drug policies over longer durations of follow-up is uncertain. Fourth we did not have the ability to look at longer-term outcomes given the issues with the changes in the coding systems. As mentioned previously, a new diagnostic coding system was implemented in Ontario hospitals as of April 2002 (ie, Ontario’s hospital systems transitioned from ICD-9 coding to ICD-10 coding). We were not confident of the translation between ICD-9 and ICD-10 coding for all of these groups of antibiotics.
the hospital codes used in our study and decided to end study follow-up in March of 2002, just before the coding transition. This decision was made to ensure consistency in coding and maximize the validity of our observations. We believe the 1-year follow-up is appropriate for 2 primary reasons. First, the impact of the restriction policy on antibiotic use was immediate and stabilized within months of implementation. Second, related hospitalizations were lim-

**Figure 4**  (A) Hospital admission rates for gastrointestinal infection-related conditions over time: quarterly rates. (B) Hospital admission rates for urinary tract infection-related conditions over time: quarterly rates. (C) Hospital admission rates for pulmonary infection-related conditions over time: quarterly rates.
ited to 4 weeks after the date of antibiotic prescription dispensing, because the majority of related clinical outcomes of antibiotic treatment are expected shortly after their use. However, we cannot comment on the sustainability of the prescribing trends beyond the 1-year follow-up period. A final limitation of our study was that we were unable to identify the specific pathogens involved in the outcomes we assessed.

Despite these limitations, the findings of this study suggest that formulary restrictions to fluoroquinolones can effectively be implemented to decrease their use without significant adverse consequences on population rates of relevant clinical outcomes. The observations of a significant reduction in the rate of hospital admissions for gastrointestinal infections, which may be a potential beneficial effect, and a significant increase in hospitalizations for urinary tract infections deserve further study to provide an explanation for these unexpected findings.

ACKNOWLEDGMENTS

We acknowledge the support and advice of the Drug Programs Branch of the Ontario Ministry of Health in conducting this study.

References

Clinical Research Study

Prevention of Central Venous Catheter-Associated Thrombosis: A Meta-analysis

Angelia Kirkpatrick, MD, MPH,a,b Suman Rathbun, MD, MS,a Thomas Whitsett, MD,a Gary Raskob, PhDb

aDepartment of Medicine, Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma City; bVeterans Affairs Medical Center, Oklahoma City; cCollege of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City.

ABSTRACT

PURPOSE: Anticoagulant prophylaxis in patients with central venous catheters is controversial. We performed a meta-analysis of randomized controlled trials of anticoagulant prophylaxis in patients with central venous catheters.

METHODS: MEDLINE and EMBASE were searched up to May 2006, supplemented by manual searches of conference proceedings and bibliographies.

RESULTS: Fifteen trials were included. Unfractionated heparin infusion, oral fixed low-dose vitamin K antagonist, and subcutaneous low-molecular-weight heparin were evaluated. For all catheter-associated deep vein thrombosis (symptomatic and asymptomatic combined), the summary relative risks ranged from 0.31 to 0.73 (all achieved statistical significance). For symptomatic deep vein thrombosis, the summary relative risks ranged from 0.28 to 0.72, but did not achieve statistical significance for any individual regimen.

CONCLUSION: Anticoagulant prophylaxis is effective for preventing all catheter-associated deep vein thrombosis in patients with central venous catheters. The effectiveness for preventing symptomatic venous thromboembolism, including pulmonary embolism, remains uncertain. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Anticoagulant; Catheter; Meta-analysis; Prophylaxis; Thrombosis; Venous

Central venous catheters are increasingly used in clinical practice, with a 27% to 67% incidence of catheter-associated deep vein thrombosis,1-3 which is most often asymptomatic. Pulmonary embolism occurs in 15% to 36% of patients with symptomatic catheter-associated deep vein thrombosis.2,3 Thus, preventive measures for catheter-associated venous thromboembolism might be warranted.

Although studies evaluating thromboembolism prophylaxis in patients with central venous catheters have been published, some report conflicting results, and evidence-based recommendations for clinical practice have varied.4,5 We performed a meta-analysis to clarify the efficacy and safety of anticoagulant administration for prevention of catheter-associated venous thromboembolism.

METHODS

We searched MEDLINE (1964 to 2006), EMBASE, and conference proceedings from The American Society of Hematology (2002 to 2005), The American Society of Clinical Oncology (1999 to 2006), and the International Society of Thrombosis and Haemostasis (2001 to 2005) using the following terms: “Thromb:.mp or hypercoag:.mp or occlu:.mp”; “anticoag:.mp or anti-vitamin k.mp or thromb: prophylax:.mp or heparin:.mp”; “catheter:.mp or cunnul:.mp or central lin:.mp or port:.mp or central venous:.mp or vascular access:.mp”; as well as generic and trade names for anticoagulants and catheters. Limits were set for human subjects and English language. Authors were contacted for additional information if required. Bibliographies were screened for relevant articles.
Objective criteria for study inclusion were defined a priori. Included were studies that: enrolled adult patients, evaluated systemically administered anticoagulant prophylaxis other than flushing of catheters with heparin or saline, evaluated prophylaxis in patients with central-venous catheters or peripherally inserted central catheters, objectively evaluated patients for deep vein thrombosis, and were randomized controlled trials.

Two reviewers (ACK, SWR) evaluated each article using predefined criteria that used established methodological standards for meta-analyses evaluating therapy.6-9 A third reviewer (TLW) resolved disagreements by blinded adjudication.

The strength and quality of each study was assessed according to the following: random and concealed group allocation; consecutive enrollment; patient spectrum; group similarity at baseline; treatment similarity other than the intervention being studied; blinding of patients, clinicians, and outcomes assessors; a priori definition of major and minor bleeding events; and use of an objective test for the evaluation of deep vein thrombosis.

The frequency of the following outcomes was recorded: all catheter-associated deep vein thrombosis; symptomatic catheter-associated deep vein thrombosis; symptomatic pulmonary embolism; major bleeding; minor bleeding; and death from all causes. Studies were included in the analysis of “all catheter-associated deep vein thrombosis” if patients underwent mandatory screening with an objective test for deep vein thrombosis. The analysis of “symptomatic catheter-associated deep vein thrombosis” included all studies that reported symptomatic events confirmed by an objective diagnostic test.

For purposes of data extraction, clinically overt bleeding was defined as major if it resulted in a decrease in hemoglobin of 2 g per deciliter or more, required the transfusion of 2 or more units of blood, was retroperitoneal, intracranial, intracoarctal, or contributed to death.10 Minor bleeding was defined as clinically overt bleeding not meeting criteria for major bleeding.

Statistical Methods
Statistical analyses adhered to established standards for meta-analysis.11-13 We assessed the validity of combining results from individual studies using the Q statistic to assess for heterogeneity.13 We considered a P value of .10 or less statistically significant evidence of heterogeneity, which, if present, would imply that the included studies estimate different population effect sizes.13 Summary relative risks for each outcome were generated using the fixed effects model, which assumes that all studies estimate the same population effect size. Analyses were repeated using the more conservative random effects model, which assumes the studies estimate different population effect sizes.13 Statistical significance of summary treatment effects was determined using a Z test, with a P value \( \leq .05 \) considered statistically significant.13

Sensitivity analyses were performed to evaluate the robustness of our results after removing individual studies from the analysis. We repeated the analyses, limiting the included studies to those that were double-blind, and those published after the year 2000. Funnel plots were generated to determine whether unpublished studies with nonsignificant results were underrepresented in our analysis, leading to publication bias that may yield overly optimistic summary relative risks.13 Calculations were performed using Comprehensive Meta-Analysis (Biostat, Inc, Englewood, NJ).

CLINICAL SIGNIFICANCE

- In patients with central venous catheters, anticoagulant prophylaxis reduces risk of all (combined symptomatic and asymptomatic) catheter-associated deep vein thrombosis.
- Effective prophylactic treatments include low-dose unfractionated heparin infusion, fixed low-dose vitamin-K antagonists, and prophylactic doses of low-molecular weight heparin.
- These treatments do not increase risk of major bleeding.
- Whether these treatments prevent symptomatic deep vein thrombosis, including pulmonary embolism, remains uncertain.

DATA SYNTHESIS

Figure 1 shows the process of study selection. The literature search identified 70 studies.14-83 Fifty-seven did not meet the predefined eligibility criteria: 24 were reviews,14-37 13 were retrospective,38-50 2 were opinions,51,52 1 was a case series,53 9 were nonconcurrently controlled,54-62 and 8 were not randomized.63-70 Thirteen were randomized71-83 and were included.

Our search of conference proceedings yielded 11 abstracts.84-94 Four were retrospective 84-87 and were excluded. Two randomized trials were excluded 88,89 due to incomplete information. Three were also published as full manuscripts and were included as such.90-92 Two remaining abstracts of randomized controlled trials were included.93-94

Study Characteristics
Table 1 (available online) shows the characteristics of 15 randomized controlled trials included for data extraction.71-83,93-94 All studies included only upper-extremity central venous catheters. Ten included only cancer patients.74-76,80-83,93,94 and 5 included only patients receiving total parenteral nutrition.71-73,78,79 Five different anticoagulant medications were evaluated: low-dose unfractionated heparin infusion, fixed low-dose vitamin-K antagonists (warfarin or acenocoumarin), and subcutaneous low-molec-
ular-weight heparins (dalteparin, enoxaparin, and nadroparin). One study compared nadroparin 2850 units daily with warfarin 1 mg daily, and one compared dalteparin 5000 units daily with acenocoumarin 1 mg daily.

**Study Quality**

Table 2 (available online) summarizes the measures of quality assessed for each study.

**All Deep Vein Thrombosis**

The results of analysis of all catheter-associated deep vein thrombosis are shown in Table 3 and Figure 2. For low-dose unfractionated heparin infusion, the summary relative risk was 0.31 (95% CI, 0.13 to 0.71). For fixed low-dose vitamin-K antagonist prophylaxis, the summary relative risk was 0.37 (95% CI, 0.26 to 0.52), and for low-molecular-weight heparin, the summary relative risk was 0.72 (95% CI, 0.57 to 0.90). No analysis demonstrated statistical evidence of heterogeneity. For studies comparing low-molecular-weight heparin to fixed low-dose vitamin-K antagonist prophylaxis, the summary relative risk was 1.88 for low-molecular-weight heparin (95% CI, 1.28 to 2.75) with no statistical evidence of heterogeneity.

**Symptomatic Deep Vein Thrombosis**

The results of the analysis for symptomatic catheter-associated deep vein thrombosis are shown in Table 4 and Figure 3. For low-dose unfractionated heparin infusion, the summary relative risk was 0.28 (95% CI, 0.05 to 1.69). For fixed low-dose vitamin-K antagonist, the summary relative risk was 0.60 (95% CI, 0.30 to 1.20). For low-molecular-weight heparin, the summary relative risk was 0.69 (95% CI, 0.30 to 1.59). The summary relative risk using any anticoagulant prophylaxis was 0.59 (95% CI, 0.35 to 0.97). There was no statistical evidence of heterogeneity.

**Pulmonary Embolism**

Five trials reported documentation of symptomatic pulmonary embolism. The summary relative risk using any anticoagulant prophylaxis for preventing symptomatic pulmonary embolism was 1.96 (95% CI, 0.52 to 7.45) with no statistical evidence of heterogeneity.

**Bleeding**

The results of the analysis for major bleeding are shown in Table 5 and Figure 4. For low-dose unfractionated heparin infusion, the summary relative risk was 0.74 (95% CI, 0.17 to 3.22). For fixed low-dose vitamin-K antagonist, the summary relative risk was 0.24 (95% CI, 0.03 to 2.13). For low-molecular-weight heparin, the summary relative risk was 0.66 (95% CI, 0.12 to 3.68). The summary relative risk of major bleeding with any anticoagulant prophylaxis was 0.54 (95% CI, 0.20 to 1.42). There was no statistical evidence of heterogeneity.

Seven studies reported minor bleeding events. For low-dose unfractionated heparin infusion, the summary relative risk was 3.74 (95% CI, 0.36 to 38.31). For fixed low-dose vitamin-K antagonist, the summary relative risk was 1.32 (95% CI, 0.87 to 2.01). The summary relative risk of minor bleeding with any anticoagulant prophylaxis was 1.40 (95% CI, 0.94 to 2.07). There was no statistical evidence of heterogeneity.

**All-Cause Mortality**

Seven trials reported documentation of all-cause mortality. For the single trial using low-dose unfractionated heparin infusion, the relative risk was 0.97 (95% CI, 0.14 to 6.67). For fixed low-dose vitamin-K antagonist prophylaxis, the summary relative risk was 0.95 (95% CI, 0.62 to 1.46). For low-molecular-weight heparin, the summary relative risk was 1.57 (95% CI, 0.94 to 2.07). There was no statistical evidence of heterogeneity.

**Sensitivity Analyses**

For low-dose unfractionated heparin infusion, the summary relative risk for symptomatic catheter-associated deep vein thrombosis in patients receiving parenteral nutrition increased from 0.28 to 1.00 (95% CI, 0.02 to 48.09) after...
removing the study in cancer patients by Abdelkefi et al. A similar analysis for all catheter-associated deep vein thrombosis did not materially alter the summary relative risk; however, the estimate no longer reached statistical significance (relative risk, 0.42; 95% CI, 0.16 to 1.06). For fixed low-dose vitamin-K antagonist, the summary relative risk for symptomatic catheter-associated deep vein thrombosis increased from 0.60 to 1.28 (95% CI, 0.45 to 3.61)

### Table 3 Relative Risk of All Catheter-Associated Deep Vein Thrombosis with Anticoagulant Prophylaxis

<table>
<thead>
<tr>
<th>Citation</th>
<th>Prophylaxis n/n (%)</th>
<th>No Prophylaxis n/n (%)</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed low-dose heparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdelkefi et al, 2004</td>
<td>1/65 (1.5)</td>
<td>8/63 (12.7)</td>
<td>0.1212</td>
<td>(0.0156-0.9409)</td>
<td>.0136</td>
</tr>
<tr>
<td>Brismar et al, 1982</td>
<td>0/23 (0)</td>
<td>4/26 (15.4)</td>
<td>0.1250</td>
<td>(0.0071-2.2036)</td>
<td>.0804</td>
</tr>
<tr>
<td>Fabr et al, 1982</td>
<td>2/24 (8.3)</td>
<td>7/22 (31.8)</td>
<td>0.2619</td>
<td>(0.0608-1.1290)</td>
<td>.0449</td>
</tr>
<tr>
<td>Fabr et al, 1984</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>1.0000</td>
<td>(0.0208-48.0855)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Macovik et al, 1984</td>
<td>2/17 (11.8)</td>
<td>1/20 (5.0)</td>
<td>2.3529</td>
<td>(0.2331-23.7458)</td>
<td>.4525</td>
</tr>
<tr>
<td>Ruggiero et al, 1983</td>
<td>0/17 (0)</td>
<td>0/17 (0)</td>
<td>1.0000</td>
<td>(0.0210-47.7081)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Fixed</td>
<td>5/166 (3.0)</td>
<td>20/168 (11.9)</td>
<td>0.3053</td>
<td>(0.1320-0.7061)</td>
<td>.0055</td>
</tr>
<tr>
<td>Random</td>
<td>5/166 (3.0)</td>
<td>20/168 (11.9)</td>
<td>0.3450</td>
<td>(0.1357-0.8771)</td>
<td>.0254</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conte et al, 2003</td>
<td>4/38 (10.5)</td>
<td>3/20 (15.0)</td>
<td>0.7018</td>
<td>(0.1738-2.8332)</td>
<td>.6191</td>
</tr>
<tr>
<td>DeCicco et al, 2006</td>
<td>46/114 (40.4)</td>
<td>63/114 (55.3)</td>
<td>0.7302</td>
<td>(0.5531-0.9638)</td>
<td>.0242</td>
</tr>
<tr>
<td>Karthaus et al, 2006</td>
<td>20/294 (6.8)</td>
<td>11/145 (7.6)</td>
<td>0.8967</td>
<td>(0.4416-1.8209)</td>
<td>.7631</td>
</tr>
<tr>
<td>Monreal et al, 1996</td>
<td>1/16 (6.3)</td>
<td>8/13 (61.5)</td>
<td>0.1016</td>
<td>(0.0145-0.7108)</td>
<td>.0014</td>
</tr>
<tr>
<td>Verso et al, 2005</td>
<td>22/155 (14.2)</td>
<td>28/155 (18.1)</td>
<td>0.7857</td>
<td>(0.4708-1.3112)</td>
<td>.3542</td>
</tr>
<tr>
<td>Fixed</td>
<td>93/617 (15.1)</td>
<td>113/447 (25.3)</td>
<td>0.7162</td>
<td>(0.5689-0.9018)</td>
<td>.0045</td>
</tr>
<tr>
<td>Random</td>
<td>93/617 (15.1)</td>
<td>113/447 (25.3)</td>
<td>0.7345</td>
<td>(0.5645-0.9557)</td>
<td>.0216</td>
</tr>
<tr>
<td>Fixed low-dose vitamin K antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bern et al, 1990</td>
<td>4/42 (9.5)</td>
<td>15/40 (37.5)</td>
<td>0.2540</td>
<td>(0.0921-0.7004)</td>
<td>.0027</td>
</tr>
<tr>
<td>DeCicco et al, 2006</td>
<td>26/120 (21.7)</td>
<td>63/114 (55.3)</td>
<td>0.3921</td>
<td>(0.2686-0.5723)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Fixed</td>
<td>30/162 (18.5)</td>
<td>78/154 (50.6)</td>
<td>0.3655</td>
<td>(0.2561-0.5217)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Random</td>
<td>30/162 (18.5)</td>
<td>78/154 (50.6)</td>
<td>0.3718</td>
<td>(0.2609-0.5300)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Fixed combined (13)</td>
<td>128/945 (13.5)</td>
<td>211/769 (27.4)</td>
<td>0.5485</td>
<td>(0.4549-0.6613)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Random combined (13)</td>
<td>128/945 (13.5)</td>
<td>211/769 (27.4)</td>
<td>0.5288</td>
<td>(0.3717-0.7522)</td>
<td>.0004</td>
</tr>
</tbody>
</table>

---

**Figure 2** Relative risk of all catheter-associated deep vein thrombosis with anticoagulant prophylaxis.
after removing the study by Bern et al.⁷⁴ For low-molecular-weight heparin, the summary relative risk for symptomatic catheter-associated deep vein thrombosis increased from 0.69 to 0.98 (95% CI, 0.35 to 2.70) after removing the study by Verso et al.⁸³ No other summary estimates of relative risk were materially altered by removal of individual studies except that some estimates failed to reach statistical significance.

Limiting the analysis of all catheter-associated deep vein thrombosis to studies that were double-blind⁷³,⁸¹-⁸³ increased the summary relative risk for low-dose unfractionated heparin infusion from 0.31 to 2.35 (95% CI, 0.23 to 23.75). For symptomatic catheter-associated deep vein thrombosis, limiting the analysis to studies that were double-blind⁸¹-⁸³ increased the summary relative risk for fixed low-dose vitamin-K antagonist from 0.60 to 1.15 (95% CI, 0.36 to 3.68) and increased the summary relative risk for any anticoagulant prophylaxis from 0.59 to 0.82 (95% CI, 0.41 to 1.62). Limiting the analysis to studies published after the year 2000⁷⁷,⁸¹,⁸³,⁹³,⁹⁴ did not materially alter any of the summary relative risks for all catheter-associated deep vein thrombosis. A similar analysis for symptomatic catheter-associated deep vein thrombosis⁷⁶,⁷⁷,⁸¹-⁸³ increased the summary relative risk using fixed low-dose vitamin-K antagonist from 0.60 to 1.28 (95% CI, 0.45 to 3.61). Further subgroup

### Table 4: Relative Risk of Symptomatic Catheter-Associated Deep Vein Thrombosis with Anticoagulant Prophylaxis

<table>
<thead>
<tr>
<th>Citation</th>
<th>Prophylaxis</th>
<th>No Prophylaxis</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed low-dose heparin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdelkafi et al, 2004⁷⁷</td>
<td>1/65 (1.5)</td>
<td>5/68 (7.4)</td>
<td>0.2092</td>
<td>(0.0251-1.7430)</td>
<td>.1063</td>
</tr>
<tr>
<td>Fabri et al, 1984⁷²</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>1.0000</td>
<td>(0.0208-48.0855)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Fixed</td>
<td>1/85 (1.2)</td>
<td>5/88 (5.7)</td>
<td>0.2826</td>
<td>(0.0473-1.6886)</td>
<td>.1659</td>
</tr>
<tr>
<td>Random</td>
<td>1/85 (1.2)</td>
<td>5/88 (5.7)</td>
<td>0.3001</td>
<td>(0.0467-1.9269)</td>
<td>.2066</td>
</tr>
<tr>
<td><strong>Low-molecular-weight heparin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karthaus et al, 2006⁸¹</td>
<td>10/293 (3.4)</td>
<td>5/145 (3.5)</td>
<td>0.9898</td>
<td>(0.3447-2.8423)</td>
<td>.9847</td>
</tr>
<tr>
<td>Monreal et al, 1996⁷⁵</td>
<td>0/16 (0)</td>
<td>0/13 (0)</td>
<td>0.8235</td>
<td>(0.0174-38.9166)</td>
<td>.9213</td>
</tr>
<tr>
<td>Verso et al, 2005⁵³</td>
<td>2/191 (1.1)</td>
<td>6/194 (3.1)</td>
<td>0.3386</td>
<td>(0.0692-1.6566)</td>
<td>.1595</td>
</tr>
<tr>
<td>Fixed</td>
<td>12/500 (2.4)</td>
<td>11/352 (3.1)</td>
<td>0.6890</td>
<td>(0.2995-1.5850)</td>
<td>.3808</td>
</tr>
<tr>
<td>Random</td>
<td>12/500 (2.4)</td>
<td>11/352 (3.1)</td>
<td>0.7177</td>
<td>(0.3047-1.6905)</td>
<td>.4480</td>
</tr>
<tr>
<td><strong>Fixed low-dose vitamin K antagonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bern et al, 1990⁷⁴</td>
<td>4/42 (9.5)</td>
<td>13/40 (32.5)</td>
<td>0.2930</td>
<td>(0.1042-0.8238)</td>
<td>.0103</td>
</tr>
<tr>
<td>Couban et al, 2005⁸²</td>
<td>6/130 (4.6)</td>
<td>5/125 (4.0)</td>
<td>1.1538</td>
<td>(0.3613-3.6849)</td>
<td>.8089</td>
</tr>
<tr>
<td>Heaton et al, 2002⁷⁶</td>
<td>2/45 (4.4)</td>
<td>1/43 (2.3)</td>
<td>1.9111</td>
<td>(0.1798-20.3173)</td>
<td>.5840</td>
</tr>
<tr>
<td>Fixed</td>
<td>12/217 (5.5)</td>
<td>19/208 (9.1)</td>
<td>0.6039</td>
<td>(0.3044-1.1983)</td>
<td>.1492</td>
</tr>
<tr>
<td>Random</td>
<td>12/217 (5.5)</td>
<td>19/208 (9.1)</td>
<td>0.6039</td>
<td>(0.2250-2.1399)</td>
<td>.5247</td>
</tr>
<tr>
<td>Fixed combined (8)</td>
<td>25/802 (3.1)</td>
<td>35/648 (5.4)</td>
<td>0.5879</td>
<td>(0.3549-0.9740)</td>
<td>.0392</td>
</tr>
<tr>
<td>Random combined (8)</td>
<td>25/802 (3.1)</td>
<td>35/648 (5.4)</td>
<td>0.6113</td>
<td>(0.3584-1.0426)</td>
<td>.0708</td>
</tr>
</tbody>
</table>

![Figure 3](image-url) Relative risk of symptomatic catheter-associated deep vein thrombosis with anticoagulant prophylaxis.
analyses did not materially alter any other summary estimates of relative risk; however, some estimates no longer reached statistical significance.

The summary estimate of the relative risk of symptomatic catheter-associated deep vein thrombosis for any anticoagulant no longer achieved statistical significance using the more conservative random-effects model (relative risk, 0.61; 95% CI, 0.36 to 1.04). Using the random-effects model did not alter the results for any other outcomes.

Funnel plots of effect size versus precision show no evidence of publication bias. A similar number of studies were distributed on either side of the summary estimate, suggesting that studies with significant and nonsignificant results were equally represented in our analysis.

**DISCUSSION**

Our results indicate that all of the anticoagulant regimens evaluated are effective for preventing all catheter-associated deep vein thrombosis with relative risk reductions of 27% to 70% (absolute risk reduction 9% to 32%) (Table 3). The results also provide suggestive evidence that anticoagulant

---

**Table 5** Relative Risk of Major Bleeding with Anticoagulant Prophylaxis

<table>
<thead>
<tr>
<th>Citation</th>
<th>Prophylaxis</th>
<th>No Prophylaxis</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed low-dose heparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdelkefi et al, 2004**</td>
<td>2/55 (3.6)</td>
<td>3/53 (5.7)</td>
<td>0.6424 (0.1118-3.6931)</td>
<td>.6168</td>
</tr>
<tr>
<td>Brismar et al, 1982**</td>
<td>0/23 (0)</td>
<td>0/26 (0)</td>
<td>1.1250 (0.0232-54.5411)</td>
<td>.9525</td>
</tr>
<tr>
<td>Fabri et al, 1984**</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>1.0000 (0.0208-48.0855)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Fixed</td>
<td>2/98 (2.0)</td>
<td>3/99 (3.0)</td>
<td>0.7432 (0.1718-3.2157)</td>
<td>.6913</td>
</tr>
<tr>
<td>Random</td>
<td>2/98 (2.0)</td>
<td>3/99 (3.0)</td>
<td>0.7427 (0.1700-3.2465)</td>
<td>.6925</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conte et al, 2003**</td>
<td>0/38 (0)</td>
<td>0/20 (0)</td>
<td>0.5385 (0.0111-26.1756)</td>
<td>.7511</td>
</tr>
<tr>
<td>Karthaus et al, 2006**</td>
<td>1/285 (0.4)</td>
<td>0/140 (0.7)</td>
<td>0.4912 (0.0310-7.7957)</td>
<td>.6069</td>
</tr>
<tr>
<td>Monreal et al, 1996**</td>
<td>0/17 (0)</td>
<td>0/15 (0)</td>
<td>0.8889 (0.0187-42.2610)</td>
<td>.9523</td>
</tr>
<tr>
<td>Verso et al, 2005**</td>
<td>0/189 (0)</td>
<td>0/193 (0)</td>
<td>1.0211 (0.0204-51.1956)</td>
<td>.9917</td>
</tr>
<tr>
<td>Fixed</td>
<td>1/529 (0.2)</td>
<td>1/368 (0.3)</td>
<td>0.6582 (0.1177-3.6802)</td>
<td>.6339</td>
</tr>
<tr>
<td>Random</td>
<td>1/529 (0.2)</td>
<td>1/368 (0.3)</td>
<td>0.6526 (0.1143-3.7265)</td>
<td>.6312</td>
</tr>
<tr>
<td>Fixed low-dose vitamin K antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Couban et al, 2005**</td>
<td>0/130 (0)</td>
<td>3/125 (2.4)</td>
<td>0.1374 (0.0072-2.6333)</td>
<td>.1208</td>
</tr>
<tr>
<td>Heaton et al, 2002**</td>
<td>0/45 (0)</td>
<td>0/43 (0)</td>
<td>0.9565 (0.0194-47.1638)</td>
<td>.9822</td>
</tr>
<tr>
<td>Fixed</td>
<td>0/175 (0)</td>
<td>3/168 (1.8)</td>
<td>0.2400 (0.0270-2.1320)</td>
<td>.2003</td>
</tr>
<tr>
<td>Random</td>
<td>0/175 (0)</td>
<td>3/168 (1.8)</td>
<td>0.2788 (0.0265-2.9347)</td>
<td>.2875</td>
</tr>
<tr>
<td>Fixed combined (9)</td>
<td>3/802 (0.4)</td>
<td>7/635 (1.1)</td>
<td>0.5356 (0.2025-1.4163)</td>
<td>.2082</td>
</tr>
<tr>
<td>Random combined (9)</td>
<td>3/802 (0.4)</td>
<td>7/635 (1.1)</td>
<td>0.5923 (0.2146-1.6350)</td>
<td>.3121</td>
</tr>
</tbody>
</table>

---

**Figure 4** Relative risk of major bleeding with anticoagulant prophylaxis.
prophylaxis is effective for preventing symptomatic catheter-associated deep vein thrombosis, based on the pooled analysis across anticoagulant regimens (Table 4). The effectiveness of any individual regimen for preventing symptomatic catheter-associated deep vein thrombosis or pulmonary embolism remains uncertain due to the small number of symptomatic events in each subgroup. Confidence intervals for the summary relative risks were broad, however, and do not exclude the possibility of a potentially clinically important benefit.

The clinical importance of asymptomatic catheter-associated deep vein thrombosis is incompletely understood, although catheter-associated deep vein thrombosis has been associated with clinically important pulmonary embolism, including fatal embolism. Anticoagulant prophylaxis, therefore, has the potential to prevent serious thromboembolic events.

Our analysis does not support the view that the materials and structure of central venous catheters have improved recently, leading to lower rates of catheter-associated thrombosis. Limiting our analysis to studies published after the year 2000 did not change the reduction in relative risk of all catheter-associated deep vein thrombosis using any anticoagulant regimen, and the observed rates of all deep vein thrombosis without prophylaxis in these studies ranged from 7.6% to 55.3%. A similar analysis for symptomatic catheter-associated deep vein thrombosis increased the summary relative risk in only one subgroup of studies evaluating fixed low-dose vitamin-K antagonists. Due to smaller combined sample sizes, 95% confidence intervals for this estimate were broad and do not exclude the potential for a clinically meaningful benefit.

Our analysis found that the absolute risk of major bleeding was low for each of the regimens (Table 5). The pooled analysis did not detect an increase in major bleeding associated with anticoagulant prophylaxis. The absolute increase in the incidences of major bleeding with anticoagulant prophylaxis compared with no prophylaxis is unlikely to be greater than 0.9% for any regimen.

Analysis of 2 randomized trials comparing fixed low-dose vitamin-K antagonist to low-molecular-weight heparin indicates that low-molecular-weight heparin is less effective for preventing all catheter-associated deep vein thrombosis than fixed low-dose vitamin-K antagonist prophylaxis (summary relative risk 1.9; 95% CI, 1.3 to 2.7). This finding is contradictory to results of recent clinical trials showing superior efficacy of low-molecular-weight heparin compared with vitamin-K antagonists for treatment of established venous thromboembolism in cancer patients, and requires further evaluation.

We did not detect a statistically significant reduction in either pulmonary embolism or all-cause mortality with anticoagulant prophylaxis. Due to the low frequency of these outcomes, 95% confidence intervals for summary relative risks were broad and did not exclude the potential for meaningful benefit. Additional randomized controlled trials evaluating these outcomes are needed.

A recently completed randomized trial compared fixed low-dose warfarin (1 mg) with either adjusted-dose warfarin (international normalized ratio 1.5 to 2.0) or no prophylaxis in cancer patients receiving chemotherapy via central venous catheters. Because the outcome data were reported for only 90% of patients, this trial was not included in our analysis. The results suggest that adjusted-dose warfarin was more effective than fixed-dose warfarin, reducing the incidence of symptomatic thrombosis from 7% to 3%; however, major bleeding increased from 2% to 4%. The observed rates of symptomatic thrombosis for fixed-dose warfarin or no prophylaxis were similar (5% and 6%, respectively, odds ratio 0.94; 95% CI, 0.52 to 1.72). The 95% confidence interval does not exclude the possibility of a clinically important benefit of fixed low-dose warfarin for preventing symptomatic thrombotic events. Because clinicians selected which patients entered into the randomized comparison of either fixed-dose warfarin versus no prophylaxis, or to the comparison of fixed versus adjusted-dose warfarin, the results may be biased against fixed low-dose warfarin if clinicians were effective at selecting patients at lower risk for thromboembolism for comparison with no prophylaxis, or patients at higher risk of thromboembolism for comparison against adjusted-dose warfarin.

Three previous systematic reviews have evaluated the efficacy of anticoagulant prophylaxis for prevention of catheter-associated deep vein thrombosis. None of these reviews included 3 randomized controlled trials that were included in our analysis.

Limitations of our meta-analysis include the potential for publication bias. Although our funnel plots did not suggest publication bias, the low number of trials makes definitive interpretation difficult. Our search strategy was comprehensive, including multiple databases, abstracts presented at national meetings, and manual searches for articles not retrieved by database searches. The overall limited number of trials retrieved, and their small sample sizes, limited our ability to precisely quantitate the efficacy of individual anticoagulant prophylaxis regimens for reducing symptomatic venous thromboembolism. In addition, tests of heterogeneity and sensitivity analyses were limited by the small number of trials. Finally, only 3 trials evaluating symptomatic outcomes were double-blinded with concealment of randomization. These limitations all support the need for additional high-quality randomized controlled trials.

In conclusion, anticoagulant prophylaxis is effective for preventing all catheter-associated deep vein thrombosis. This finding is driven primarily by a reduction in asymptomatic thrombi detected by mandatory screening for deep vein thrombosis. The effectiveness of individual anticoagulant regimens for preventing symptomatic venous thromboembolism, including pulmonary embolism, remains uncertain. Based on the available evidence, the risk-benefit of anticoagulant prophylaxis for preventing clinically impor-
tant venous thromboembolic events is uncertain. With increasing central venous catheter use, there is a need for large rigorous randomized trials to resolve this issue. Currently, the decision to use anticoagulant prophylaxis remains a clinical judgment based on the estimated risks of thromboembolism and major bleeding in the individual patient.

References
8. Guyatt GH, Sackett DL, Cook DJ. Users’ guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA. 1993;270(21):2598-2601.
9. Guyatt GH, Sackett DL, Cook DJ. Users’ guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA. 1994;271(1):59-63.


<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Sample Size</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Catheter Type Where Inserted</th>
<th>Vein Where Inserted</th>
<th>Duration Catheterization</th>
<th>Onset Prophylaxis</th>
<th>Duration Prophylaxis</th>
<th>Prophylaxis Continuous</th>
<th>Length of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabri et al, 1982</td>
<td>46</td>
<td>Heparin</td>
<td>3000 USP units/L IV</td>
<td>With TPN</td>
<td>Central line</td>
<td>Subclavian</td>
<td>After insertion</td>
<td>Not clear</td>
<td>After insertion</td>
<td>Not clear</td>
<td>Not Clear</td>
<td>Not Clear</td>
</tr>
<tr>
<td>Fabri et al, 1984</td>
<td>40</td>
<td>Heparin</td>
<td>3000 units/L IV</td>
<td>With TPN</td>
<td>Central line</td>
<td>Subclavian</td>
<td>22.1 ± 3.2 days</td>
<td>After insertion</td>
<td>At insertion</td>
<td>7-94 days (mean 25 days)</td>
<td>No</td>
<td>22.1 ± 3.2 days</td>
</tr>
<tr>
<td>Brismar et al, 1982</td>
<td>49</td>
<td>Heparin</td>
<td>5000 U IV</td>
<td>Every 6 hours</td>
<td>PICC</td>
<td>External jugular</td>
<td>Subclavian</td>
<td>7-94 days (mean 25 days)</td>
<td>Not clear</td>
<td>Yes</td>
<td>22.1 ± 3.2 days</td>
<td>&gt;14 days in 18 patients</td>
</tr>
<tr>
<td>Ruggiero et al, 1983</td>
<td>34</td>
<td>Heparin</td>
<td>1000 U/L IV</td>
<td>With TPN</td>
<td>Central line</td>
<td>Subclavian</td>
<td>&gt;14 days in 18 patients</td>
<td>Not clear</td>
<td>7-43 days (mean 18 days)</td>
<td>Yes</td>
<td>8 Weeks after removal</td>
<td></td>
</tr>
<tr>
<td>Macovsik et al, 1984</td>
<td>37</td>
<td>Heparin</td>
<td>1 unit/mL IV</td>
<td>With TPN</td>
<td>Central line</td>
<td>Subclavian</td>
<td>At least 4 weeks</td>
<td>After insertion</td>
<td>Not clear</td>
<td>Yes</td>
<td>90 days or DVT</td>
<td>90 days</td>
</tr>
<tr>
<td>Abdelkefi et al, 2004</td>
<td>108</td>
<td>Heparin</td>
<td>100 IU/Kg/D IV</td>
<td>Continuous infusion</td>
<td>Central line</td>
<td>Subclavian</td>
<td>8-81 days</td>
<td>No</td>
<td>8 weeks after removal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bern et al, 1990</td>
<td>121</td>
<td>Warfarin</td>
<td>1 mg PO daily</td>
<td>Tunneled</td>
<td>Subclavian</td>
<td>Not stated</td>
<td>Before insertion</td>
<td>90 days or DVT</td>
<td>Mean 41 days</td>
<td>No</td>
<td>90 days</td>
<td></td>
</tr>
<tr>
<td>Heaton et al, 2006</td>
<td>98</td>
<td>Warfarin</td>
<td>1 mg PO daily</td>
<td>Tunneled</td>
<td>Subclavian</td>
<td>30 Lines removed before 90 days</td>
<td>At insertion</td>
<td>90 days</td>
<td>3 months after line removed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Couban et al, 2005</td>
<td>255</td>
<td>Warfarin</td>
<td>1 mg PO daily</td>
<td>Tunneled, PICC, port</td>
<td>Subclavian, basilic, cephalic</td>
<td>Subclavian</td>
<td>Median 25 weeks</td>
<td>After insertion</td>
<td>Median 8 weeks</td>
<td>No</td>
<td>3 months after line removed</td>
<td></td>
</tr>
<tr>
<td>Monreal et al, 1996</td>
<td>29</td>
<td>Dalteparin</td>
<td>2500 units SC daily</td>
<td>Tunneled</td>
<td>Subclavian</td>
<td>Not stated</td>
<td>Before insertion</td>
<td>90 days or DVT</td>
<td>Yes</td>
<td>7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conte et al, 2003</td>
<td>58</td>
<td>Dalteparin</td>
<td>5000 IU SC daily</td>
<td>Central line</td>
<td>Subclavian, &amp; LJ</td>
<td>Subclavian</td>
<td>&gt;1 week</td>
<td>No</td>
<td>Yes</td>
<td>7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verso et al, 2005</td>
<td>310</td>
<td>Enoxaparin</td>
<td>40 mg SC daily</td>
<td>Tunneled, PICC</td>
<td>Subclavian, LJ and EJ</td>
<td>Subclavian</td>
<td>42 ± 2 days</td>
<td>Before insertion</td>
<td>42 ± 2 days</td>
<td>Yes</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Karthaus et al, 2006</td>
<td>425</td>
<td>Dalteparin</td>
<td>5000 IU SC daily</td>
<td>Not clear</td>
<td>Subclavian</td>
<td>At least 12 weeks</td>
<td>Before insertion</td>
<td>Within 5 days of insertion</td>
<td>16 weeks</td>
<td>Yes</td>
<td>16 weeks</td>
<td></td>
</tr>
<tr>
<td>Mismetti et al, 2003</td>
<td>59</td>
<td>Nadroparin vs Warfarin</td>
<td>2850 units vs 1 mg SC and PO daily</td>
<td>Tunneled, Subclavian and LJ</td>
<td>Subclavian</td>
<td>90 days except for 12 caths &lt;90 days</td>
<td>Before insertion</td>
<td>90 ± 5 days or DVT</td>
<td>For first 90 days, yes</td>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeCicco et al, 2006</td>
<td>450</td>
<td>Dalteparin vs Acenocumarine vs Control</td>
<td>5000 units vs 1 mg vs No Prophylaxis SC and PO Daily</td>
<td>Not clear</td>
<td>Subclavian and IJ</td>
<td>Not clear</td>
<td>At least 12 weeks</td>
<td>Before insertion</td>
<td>Before insertion</td>
<td>8 days</td>
<td>Not clear</td>
<td>Not clear</td>
</tr>
</tbody>
</table>

USP = United States Pharmacopeial Convention; L = liter; U = units; mL = milliliter; IU = international units; Kg = kilogram; D = day; mg = milligram; IV = intravenously; PO = orally; SC = subcutaneously; TPN = total parenteral nutrition; PICC = peripherally inserted central catheter; LJ = internal jugular; EJ = external jugular; DVT = deep venous thrombosis.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Drug</th>
<th>Consecutive Enrollment</th>
<th>Randomization Concealed</th>
<th>Similar at Baseline</th>
<th>Treated Similarly</th>
<th>Patient Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabri et al, 1982⁷¹</td>
<td>Heparin</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
<td>Not clear</td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>Fabri et al, 1984⁷²</td>
<td>Heparin</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
<td>Not clear</td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>Brismar et al, 1982⁷⁸</td>
<td>Heparin</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
<td>Not clear</td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>Ruggiero et al, 1983⁷⁹</td>
<td>Heparin</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
<td>Not clear</td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>Macoviak et al, 1984⁷³</td>
<td>Heparin</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
<td>Yes</td>
<td>Parenteral nutrition or hematologic disorders, age &lt;60</td>
</tr>
<tr>
<td>Abdelkefi et al, 2004⁷⁷</td>
<td>Heparin</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
<td>Yes</td>
<td>Parenteral nutrition or hematologic disorders, age &lt;60</td>
</tr>
<tr>
<td>Bern et al, 1990⁷⁴</td>
<td>Warfarin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Not clear</td>
<td>Hematologic cancer</td>
</tr>
<tr>
<td>Heaton et al, 2002⁷⁶</td>
<td>Warfarin</td>
<td>Yes</td>
<td>No</td>
<td>Not clear</td>
<td>Yes</td>
<td>Cancer</td>
</tr>
<tr>
<td>Couban et al, 2005⁸²</td>
<td>Warfarin</td>
<td>Not clear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Cancer</td>
</tr>
<tr>
<td>Monreal et al, 1996⁷⁵</td>
<td>Dalteparin</td>
<td>Yes</td>
<td>Not clear</td>
<td>Yes</td>
<td>Not clear</td>
<td>Cancer</td>
</tr>
<tr>
<td>Conte et al, 2003⁹³</td>
<td>Dalteparin</td>
<td>Not clear</td>
<td>No</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Cancer</td>
</tr>
<tr>
<td>Verso et al, 2005⁸³</td>
<td>Enoxaparin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Cancer</td>
</tr>
<tr>
<td>Karthaus et al, 2006⁸¹</td>
<td>Dalteparin</td>
<td>Not clear</td>
<td>Yes</td>
<td>Yes</td>
<td>Not clear</td>
<td>Cancer</td>
</tr>
<tr>
<td>Mismetti et al, 2003⁸⁰</td>
<td>Nadroprin vs warfarin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Cancer</td>
</tr>
<tr>
<td>DeCicco et al, 2006⁸⁴</td>
<td>Dalteparin vs Acenocumarine vs control</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Cancer</td>
</tr>
</tbody>
</table>
AJM Online

AJM Online is a special section of *The American Journal of Medicine*, which provides additional original research and reviews via the Internet. Every month, new peer-reviewed articles covering important medical advances are published in AJM Online. These articles are indexed in *Index Medicus*, *ScienceDirect*, and *MEDLINE*, among other services. Abstracts from AJM Online submissions appear in every issue of *The American Journal of Medicine* in this section. The complete original articles are available only online.

**REVIEW**

Diagnostic Evaluation of Mononucleosis-Like Illnesses

Hurt C.\(^a\) Tammaro D.\(^b\)

\(^a\)Department of Medicine, Division of Infectious Diseases, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC; \(^b\)Department of Medicine, Division of General Internal Medicine, Brown Medical School, Providence, RI.

Clinicians face a diagnostic challenge when a patient with the classic fever, pharyngitis, and lymphadenopathy triad of infectious mononucleosis has a negative “spot” heterophile antibody test. This screening test, although commonly considered sensitive for the presence of Epstein-Barr virus (EBV) infection, may be negative early after infection. A growing number of pathogens have been reported to cause heterophile-negative mononucleosis-like illnesses, including cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), human immunodeficiency virus (HIV), adenovirus, herpes simplex virus (HSV), *Streptococcus pyogenes*, and *Toxoplasma gondii*. Other infectious and noninfectious disorders also may present in ways that mimic mononucleosis, but fail to generate EBV’s archetypal triad of clinical findings. A systematic approach to the diagnosis of mononucleosis-like illnesses ensures that conditions warranting specific therapy are distinguished from others requiring only supportive care.

**CLINICAL RESEARCH STUDY**

Incidence and Clinical Spectrum of Thiazide-associated Hypercalcemia

Wermers RA.\(^a\) Kearns AE.\(^a\) Jenkins GD.\(^b\) Melton LJ III.\(^a,c\)

\(^a\)Division of Endocrinology, Department of Medicine, and \(^b\)Divisions of Biostatistics and \(^c\)Epidemiology, Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minn.

**PURPOSE:** The study determines the incidence of thiazide-associated hypercalcemia and clarifies its clinical features and natural history.

**METHODS:** In a population-based descriptive study, Olmsted County, Minn, residents with thiazide-associated hypercalcemia were identified through the Rochester Epidemiology Project and the Mayo Clinic Laboratory Information System. Changes in incidence rates were evaluated by Poisson regression.

**RESULTS:** Seventy-two Olmsted County residents (68 women and 4 men; mean age, 64 years) with thiazide-associated hypercalcemia first recognized in 1992 to 2001 were identified. The overall annual age- and sex-adjusted (to 2000 US whites) incidence was 7.7 (95% confidence interval [CI], 5.9-9.5) per 100,000. There was an increase in incidence after 1996, peaking at 16.3 (95% CI, 8.3-24.3) per 100,000 in 1998. The highest rate was 55.3 per 100,000 in 70- to 79-year-old women. Hypercalcemia was identified a mean of 6 ± 7 years after thiazide initiation, and the average highest serum calcium was 10.7 ± 0.3 mg/dL with serum parathyroid hormone (obtained in 53 patients) of 4.8 ± 2.7 pmol/L. Of 33 patients who discontinued the thiazide, 21 (64%) had persistent hypercalcemia. Patients subsequently diagnosed with primary hyperparathyroidism had the highest average serum calcium and parathyroid hormone levels of 11.0 ± 0.3 mg/dL and 6.3 ± 2.4 pmol/L, respectively.

**CONCLUSION:** The persistence of hypercalcemia in patients discontinuing thiazides, and similarities in the clinical spectrum, suggest that underlying primary hyperparathyroidism is common in patients who develop hypercalcemia while taking thiazide diuretics.

**ERRATUM**


The APM Perspectives article in the August issue of the *Journal* was inadvertently published without the author’s corrections. The corrected version now appears online at http://www.amjmed.com.
<table>
<thead>
<tr>
<th>Patients Blinded</th>
<th>Clinicians Blinded</th>
<th>Outcomes Assessors Blinded</th>
<th>Method Thrombus Detection</th>
<th>Major Bleeding Defined</th>
<th>Minor Bleeding Defined</th>
<th>All Patients Accounted For</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not clear</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Venogram all patients</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>Not clear</td>
<td>Venogram all patients</td>
<td>Not clear</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Not clear</td>
<td>Yes</td>
<td>Yes</td>
<td>Venogram all patients</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Not clear</td>
<td>Yes</td>
<td>Ultrasound all patients</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Ultrasound or venogram</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Not clear</td>
<td>Yes</td>
<td>Venogram all patients</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Echo-Doppler all patients</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>Not clear</td>
<td>Yes</td>
<td>Venogram all patients</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Not clear</td>
<td>Ultrasound and venogram</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Not clear</td>
<td>Yes</td>
<td>Venogram all patients</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Not clear</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Venogram all patients</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Not clear</td>
</tr>
</tbody>
</table>
Diagnostic Evaluation of Mononucleosis-Like Illnesses

Christopher Hurt, MD,a Dominick Tammaro, MDb

aDepartment of Medicine, Division of Infectious Diseases, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC; bDepartment of Medicine, Division of General Internal Medicine, Brown Medical School, Providence, RI.

ABSTRACT

Clinicians face a diagnostic challenge when a patient with the classic fever, pharyngitis, and lymphadenopathy triad of infectious mononucleosis has a negative “spot” heterophile antibody test. This screening test, although commonly considered sensitive for the presence of Epstein-Barr virus (EBV) infection, may be negative early after infection. A growing number of pathogens have been reported to cause heterophile-negative mononucleosis-like illnesses, including cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), human immunodeficiency virus (HIV), adenovirus, herpes simplex virus (HSV), Streptococcus pyogenes, and Toxoplasma gondii. Other infectious and noninfectious disorders also may present in ways that mimic mononucleosis, but fail to generate EBV’s archetypal triad of clinical findings. A systematic approach to the diagnosis of mononucleosis-like illnesses ensures that conditions warranting specific therapy are distinguished from others requiring only supportive care. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Acute retroviral syndrome; Cytomegalovirus; Epstein-Barr virus; Human herpesvirus 6; Human immunodeficiency virus; Infectious mononucleosis; Mononucleosis-like illness; Toxoplasmosis

A 26-year-old graduate student presents with a 2-day history of fever, headache, and sore throat. She denies any rhinorrhea, cough, or sick contacts. Physical examination reveals slight tachycardia with normal temperature and blood pressure. Diffuse erythema of the pharynx is noted without tonsillar exudates. Her lungs are clear bilaterally. Rapid pharyngeal testing for group A streptococcal antigen is negative, and supportive care is advised. She returns several days later with a fever of 38.9°C, persistent pharyngeal erythema, and scattered tender anterior cervical lymph nodes. The tip of the spleen is palpable. A heterophile antibody test for Epstein-Barr virus-induced infectious mononucleosis is negative. How should you proceed?

INFECTIOUS MONONUCLEOSIS

Although the clinical triad of pharyngitis, fever, and lymphadenopathy was first described in 1889 as “glandular fever,” it was not until 1920 that the first formal definition of infectious mononucleosis (IM) was made.1 Examination of the peripheral blood smears of 6 college students presenting with glandular fever revealed striking similarities: an absolute lymphocytosis, with atypically abundant cytoplasm in many mononuclear cells. In 1932, Paul and Bunnell discovered that serum from patients with IM caused sheep erythrocytes to agglutinate, and their so-called “heterophile” antibody test became the basis for serologic diagnosis of infectious mononucleosis.2

When a laboratory worker infected with the newly discovered Epstein-Barr virus (EBV) in 1968 developed clinical symptoms of IM and heterophile antibodies,3 the cause of the disease was finally identified. EBV accounts for approximately 9 of every 10 clinical presentations suggestive of IM, and 25% to 30% of adolescents and adults up to age 30 years with primary EBV infection will fall ill.4 In contrast, childhood infection is generally subclinical. Within industrialized societies, lower socioeconomic status groups are infected with EBV at younger ages than affluent groups;5 whites in the United States are 30 times more likely than blacks to develop IM.6 More than 90% of adults worldwide who are seropositive for EBV have lifetime latent viral infection of their B lymphocytes and persistent viral shedding into saliva—the most probable source for transmission.7 The diagnosis of “infectious mononucleosis” is reserved

Requests for reprints should be addressed to Dominick Tammaro, MD, Rhode Island Hospital, Jane Brown Ground, Suite 0100, 593 Eddy Street, Providence, RI 02903.
E-mail address: dtammaro@lifespan.org

0002-9343/$ -see front matter © 2007 Elsevier Inc. All rights reserved.
for the syndrome caused by EBV, and similar presentations caused by other processes should be referred to as “mononucleosis-like illnesses” (MLI).

Clinical Presentation
In IM, the subacute onset of pharyngitis is accompanied by moderate-to-high fevers (≥37.5°C) and generalized lymphadenopathy. Up to 25% of patients have petechiae of the palate at least transiently, and the majority have pharyngeal erythema noted on examination. An evaluation of 70 different clinical signs and symptoms of IM showed that only 4 occurred statistically more often in patients with a positive heterophile antibody test: petechiae of the palate, and adenopathy in the inguinal, axillary, and posterior auricular lymph node groups. Among patients over age 40 years presenting with IM, cervical lymphadenopathy is observed with a much lower incidence, whereas hepatomegaly and jaundice are more common.

Lymphadenopathy in IM is typically symmetric, moderately tender, and tends to peak during the first week of symptoms. Mild-to-moderate tonsillar enlargement is common, frequently with grayish exudates. In general, urticarial and maculopapular rashes are rare except among those patients given beta-lactam antibacterials erroneously, 90% of whom go on to develop a rash.

A palpably enlarged spleen may be present in as many as 63% of patients. In a study of 29 patients hospitalized on an otolaryngological service for severe IM, all were found to have splenomegaly ultrasonographically, but only 17% had a palpable spleen on physical examination. Spontaneous atraumatic splenic rupture is an exceedingly rare complication of IM.

Diagnosis of IM: The Heterophile Antibody Test
The Paul-Bunnell heterophile antibody (HetAb) is actually a heterogeneous group of mostly IgM-class immunoglobulins generated in response to acute EBV infection. Immunologic studies suggest that the Paul-Bunnell antigen is actually a complex glycoprotein structure on the surface of EBV-infected cells. Structurally similar epitopes on nonhuman erythrocytes cross-react with HetAb, forming the basis of the red cell agglutination test. Absorbing other nonheterophile antibodies from patient serum with guinea pig kidney cells improves the specificity of these assays, with even greater gains seen when horse erythrocytes are used instead of those of sheep. Development of a slide-based test using equine erythrocytes resulted in the “spot” test.

Of the adolescents and adults who develop clinical IM, up to 85% have detectable HetAb. The antibodies develop within the first 7 days after the onset of symptoms, peak between 2 and 5 weeks into illness, and can be detected at low levels up to 12 months later. The heterophile test may be falsely negative in up to 25% of patients in the first week of symptoms, when antibody levels are below the limit of detection of the assay. Although heterophile testing in the pediatric population may miss 50% to 75% of acute EBV infections, it remains an excellent test for adolescents and adults, with the capability to detect between 71% and 90% of cases. Nearly 1 in 10 adults with true IM will be persistently heterophile-negative, but can be diagnosed by detection of IgM antibodies against the viral capsid antigen (VCA) of EBV. Many of these patients are at the extremes of age.

Because of the excellent specificity of current heterophile tests for IM, a positive result is generally considered definitive for the diagnosis of acute EBV infection. However, reports of EBV-negative, heterophile-positive patients presenting with symptomatic, acute infection from human immunodeficiency virus, type 1 (HIV-1) are important to bear in mind.

HETEROFILE-NEGATIVE MONONUCLEOSIS-LIKE ILLNESSES
Heterophile-negative conditions with a clinical presentation similar to IM (Table 1) can be grouped into 3 principal categories: non-EBV viral etiologies, bacterial infections, and protozoal causes. Although some literature discusses systemic disorders such as sarcoidosis and malignancies like Hodgkin’s disease as causes of MLI (Table 2), their inclusion is based mostly on the presence of a particular finding, such as atypical lymphocytosis or adenopathy, rather than the classic triad of IM’s physical findings—and they thus fall outside the scope of this review.

Viral Causes
Cytomegalovirus. Cytomegalovirus (CMV) causes an estimated 7% of MLI cases. A herpesvirus relative of EBV, CMV establishes latent infection in a substantial portion of the general population and may reactivate with immune compromise. Adolescents and adults in close contact with children under age 2 years, including daycare workers and
<table>
<thead>
<tr>
<th>Agent</th>
<th>Associated Condition(s)</th>
<th>Estimated Proportion of MLI Presentations*</th>
<th>Distinguishing Features</th>
<th>Diagnostic Test(s) for Acute Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr Virus (EBV)</td>
<td>Infectious mononucleosis</td>
<td>50%-90%</td>
<td>Tender inguinal, axillary, or posterior auricular LAD&lt;br&gt;Petechiae of palate&lt;br&gt;Tonsillar enlargement&lt;br&gt;Splenomegaly&lt;br&gt;Adolescents and adults up to age 30 Higher socioeconomic status in childhood</td>
<td>Heterophile (“spot”) test&lt;br&gt;EBV anti-VCA IgM, IgG</td>
</tr>
<tr>
<td>Human Herpesvirus 6 (HHV-6)</td>
<td>Roseola infantum (Exanthem subitum)</td>
<td>9%</td>
<td>Bilateral, nontender, anterior and posterior LAD lasting up to 3 months</td>
<td>Anti-HHV-6 IgM and IgG&lt;br&gt;HHV-6 PCR</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Mononucleosis-like illness</td>
<td>5%-7%</td>
<td>Anicteric hepatitis&lt;br&gt;Prolonged fevers&lt;br&gt;Mild cervical LAD&lt;br&gt;Contact with children, especially younger than age 2 years</td>
<td>Anti-CMV IgM&lt;br&gt;Spin amplified urine culture for CMV, with pp65 antigen detection&lt;br&gt;CMV PCR</td>
</tr>
<tr>
<td>Herpes Simplex Virus, Type 1 (HSV-1)</td>
<td>Herpes labialis</td>
<td>6%</td>
<td>Gingivostomatitis, tonsillar exudates&lt;br&gt;Profound odynophagia</td>
<td>Slide-based DFA&lt;br&gt;Viral throat culture</td>
</tr>
<tr>
<td>Group A, β-hemolytic Streptococcus pyogenes (GABHS)</td>
<td>Pharyngitis&lt;br&gt;Rheumatic fever</td>
<td>3%-4%</td>
<td>Abrupt onset of sore throat&lt;br&gt;Tonsilopharyngeal erythema&lt;br&gt;Tender, enlarged anterior cervical LAD&lt;br&gt;Absence of hepatomegaly or splenomegaly&lt;br&gt;Winter and early spring peak incidence</td>
<td>RADT&lt;br&gt;Bacterial throat culture</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>Toxoplasmosis</td>
<td>≤3%</td>
<td>Small, symmetric, nontender LAD&lt;br&gt;History of ingesting undercooked meat&lt;br&gt;Exposure to cats or cat droppings</td>
<td>Anti-Toxoplasma IgM&lt;br&gt;Anti-Toxoplasma IgG&lt;br&gt;ELISA and/or avidity assay</td>
</tr>
<tr>
<td>Human Immunodeficiency Virus, Type 1 (HIV-1)</td>
<td>Acute retroviral syndrome (ARS)&lt;br&gt;AIDS</td>
<td>≤2%</td>
<td>Abrupt onset of symptoms, lasting up to 2 weeks&lt;br&gt;Painful mucocutaneous ulcers on oral mucosa, penis, or anus&lt;br&gt;Nontender axillary, cervical, and occipital LAD between 7 and 14 days&lt;br&gt;Nonpruritic, macular or maculopapular exanthem generalizing from face, chest to extremities—including palms and soles&lt;br&gt;Intravenous drug use, unprotected sexual intercourse, or other HIV exposure risks</td>
<td>ELISA with Western blot&lt;br&gt;HIV-1 PVL</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Nonspecific upper respiratory symptoms&lt;br&gt;Pharyngo-conjunctival fever&lt;br&gt;Pneumonia</td>
<td>≤1%</td>
<td>Clinically similar to GABHS&lt;br&gt;Conjunctivitis may accompany pharyngitis</td>
<td>EIA&lt;br&gt;Viral culture of conjunctivae or throat&lt;br&gt;Shell vial culture of throat or nasopharyngeal secretions</td>
</tr>
</tbody>
</table>

AIDS = acquired immune deficiency syndrome; DFA = direct fluorescent antibody; EIA = enzyme immunoassay; ELISA = enzyme-linked immunosorbent assay; LAD = lymphadenopathy; PCR = polymerase chain reaction; PVL = plasma viral load; RADT = rapid antigen detection test; VCA = viral capsid antigen.

*Data from: 23, 47, 52, 60.
schoolteachers, are at higher risk of acute CMV infection. Although primary infection is usually asymptomatic, CMV can produce a MLI difficult to distinguish clinically from IM. Sore throat, fatigue, and malaise are prominent in both, although the degree of lymphadenopathy, pharyngeal erythema, and splenomegaly is generally less with CMV. Non-specific rashes also may be seen.

Unlike IM, elevated transaminases are frequent in CMV-induced MLI, occurring in up to 92% of cases. Although this sometimes causes confusion with more typical forms of viral hepatitis, the increase in transaminase levels rarely exceeds 5-fold above normal—in sharp contrast to the increases as high as 100-fold seen with classic hepatitis viruses. Assays for anti-CMV IgM antibodies, generally positive during acute infection, have been replaced as the diagnostic test of choice by antigen detection assays. In the late 1980s detection of p24, the capsid protein, proved particularly useful. However, with inferior sensitivity to PVL and false-negative results in almost 25% of patients with ARS, p24 antigen testing has fallen out of favor. Although not yet licensed by the Food and Drug Administration (FDA) for the diagnosis of ARS, reverse transcriptase polymerase chain reaction (RT-PCR) PVL testing appears to be highly sensitive and specific for acute infection.

**Human Immunodeficiency Virus, Type 1.** The acute retroviral syndrome (ARS) of symptomatic early HIV-1 infection was first described as a MLI in 1985. Approximately 90% of patients develop ARS within 6 months of acquiring HIV, and many are ill enough to seek medical attention. Symptoms develop abruptly after an average incubation time of 2 to 4 weeks and may include sore throat, myalgia, arthralgia, headache, malaise, and nausea. Fever may be as high as 40°C and accompanied by pharyngitis and nontender lymphadenopathy of the axillary, cervical, and occipital nodes. Mucocutaneous ulceration may be seen in primary HIV-1 infection, with well-demarcated, painful, shallow ulcers of the oral mucosa, penis, or anus. A nonpruritic, maculopapular rash is common in ARS. Developing 48 to 72 hours after the onset of fever and lasting up to a week, the exanthem erupts on the face and upper chest before spreading to the extremities, including the palms and soles.

Standard enzyme-linked immunosorbent assays (ELISAs) detect the presence of HIV-specific antibodies from clinical specimens. Serum is incubated in wells of a microtiter plate containing immobilized HIV antigens, allowing any antibodies present in the serum to bind to their corresponding antigens. A second, assay-specific, enzyme-conjugated immunoglobulin is then added, which attaches to any plate-bound patient antibodies. The enzyme’s activity is measured, serving as a proxy for the amount of original anti-HIV antibody present in the patient’s serum. Typically, anti-HIV antibodies do not reach a detectable level for about 2 weeks after infection, so ELISAs therefore cannot be relied upon to diagnose ARS.

Because initial, unchecked replication of HIV-1 in a new host leads to high levels of viremia, HIV antigen assays were used to detect acute infection before the advent of widespread plasma viral load (PVL) testing. One antigen in particular, a structural protein of the viral capsid named p24, proved particularly useful. However, with inferior sensitivity to PVL and false-negative results in almost 25% of patients with ARS, p24 antigen testing has fallen out of favor. Although not yet licensed by the Food and Drug Administration (FDA) for the diagnosis of ARS, reverse transcriptase polymerase chain reaction (RT-PCR) PVL testing appears to be highly sensitive and specific for this purpose. False-positive RT-PCR results have been reported at a rate of about 2% to 3%, and are suggested in those patients with less than 2000 copies of HIV-1 RNA per cubic centimeter of blood (copies/cc). If ARS is strongly
suspected and the PVL result is <10,000 copies/cc, the test should be repeated.\textsuperscript{42}

**Adenovirus.** A common cause of self-limited childhood respiratory tract infections, adenovirus is often more aggressive among adults. Spread by aerosols or fecal-oral transmission, the virus is hearty and can survive for long periods outside of the host. Pharyngitis and coryza are common presentations of infection, often accompanied by fever and cervical lymphadenopathy.\textsuperscript{43} When conjunctivitis is present as well, the findings mark one of the classic syndromes of adenoviral infection, pharyngoconjunctival fever—large outbreaks of which have been associated with public swimming pools. Adults may develop tracheobronchitis or a mild atypical pneumonia, although manifestations are often more severe among immunosuppressed patients.\textsuperscript{44} Enzyme immunoassay (EIA) and PCR-based rapid diagnostic methods are available,\textsuperscript{45,46} but the reference standard remains isolation of the virus in culture from nasopharyngeal or oropharyngeal secretions.

**Herpes Simplex Virus, Type 1.** Although the “cold sore” of herpes simplex virus, type 1 (HSV-1) is thought to be its major clinical manifestation, herpes labialis actually represents reactivation disease. Pharyngitis, tonsillar exudates, and gingivostomatitis are the most frequent manifestations of primary herpetic infection.\textsuperscript{46} A study of over 600 college students demonstrated HSV-1 to be the cause of pharyngitis in almost 6\% of cases.\textsuperscript{47} Although fever and odynophagia are present for 3 to 8 days, cervical lymphadenopathy may continue for several weeks. Serologic techniques require comparison of acute and convalescent sera, and have a limited role in diagnosing acute infection. Rapid detection of HSV is possible with various ELISA and PCR-based methods.\textsuperscript{48} From studies of genital ulcerative disease, PCR has proven to be both faster and more sensitive than traditional viral culture.\textsuperscript{49}

**Bacterial Causes**

**Streptococcus pyogenes.** Group A β-hemolytic *Streptococcus pyogenes* (GABHS) is the most frequent bacterial cause of acute pharyngitis.\textsuperscript{50} Most cases of “strep throat” occur in the winter or early spring months in temperate climates. Among all adults presenting with sore throat, GABHS accounts for up to 10\% of cases.\textsuperscript{51} Streptococcal illness is more likely among patients who have significant contact with school-aged children, especially those between 5 and 15 years of age. In 2 large studies of patients evaluated for MLI, rates of GABHS-associated pharyngitis were <5\%.\textsuperscript{52,53}

Streptococcal pharyngitis presents with the abrupt onset of fever and intense odynophagia. Physical examination generally reveals hyperemia of the pharynx, with or without exudates. Erythema and edema of the uvula and soft palate may be seen, occasionally with petechiae. Anterior cervical lymph nodes may become enlarged and tender. Throat culture remains the diagnostic standard, with a sensitivity of 90\% to 95\% if properly collected.\textsuperscript{54} Although rapid antigen detection tests (RADTs) are not as sensitive as throat culture, their specificity for GABHS significantly increases the number of patients treated appropriately with antibiotics.\textsuperscript{55} Because of the low incidence of GABHS pharyngitis among adults, current recommendations suggest that a confirmatory throat culture is not necessary if the RADT is negative.\textsuperscript{56}

**Protozoal Causes**

**Toxoplasma gondii.** Toxoplasmosis is the main protozoal cause of MLI. The life cycle of *Toxoplasma gondii* can only be completed through sexual replication in the feline intestinal tract; the host cat sheds oocysts in its feces.\textsuperscript{57} Shortly after ingestion by other animals, oocysts transform into freely motile tachyzoites that invade gut epithelium and disseminate. Tachyzoites tend to localize in brain and muscle tissue, encyst, and lay dormant for the life of the host. In most of the world, ingestion of undercooked meat containing *T. gondii* cysts appears to be the major vector for transmission.\textsuperscript{57}

Immunocompetent patients with primary *T. gondii* infection are often asymptomatic, but nontender cervical or occipital lymphadenopathy is sometimes seen.\textsuperscript{58} Constitutional symptoms are mild. Maculopapular rashes, pharyngitis, and hepatosplenomegaly also occur, but much less frequently. Toxoplasmosis is generally self-limited, resolving spontaneously over several months. Diagnosis of acute infection in pregnancy is particularly important, as toxoplasmosis may cause damage to the developing fetal nervous system.\textsuperscript{58}

Because anti-toxoplasma IgM antibodies can persist for years after infection, their presence alone cannot be used to diagnose primary infection. The same is true for anti-toxoplasma IgG antibodies, which appear within 2 weeks of primary infection and remain detectable for life.\textsuperscript{58} Acute versus chronic infection may be distinguished by IgG “avidity” testing, based on the finding that prolonged immunologic exposure to the organism results in the production of anti-toxoplasma IgG antibodies with progressively stronger binding to (or avidity for) toxoplasmal antigens. Thus, in a patient with a positive IgM, weaker binding of IgG in an avidity assay is suggestive of more recent infection.\textsuperscript{59}

**Approach to Diagnosis**

Given the array of conditions mimicking infectious mononucleosis (Table 1), a systematic approach to heterophile-negative mononucleosis-like illness is essential. Before embarking on any laboratory assessment, a comprehensive history should be obtained from the patient, including past medical problems, family history, contact with pets or with any sick persons, sexual history, and any recent travel. Although physical examination may reveal only nonspecific findings, the discovery of characteristic features of some diseases—such as mucocutaneous ulceration in acute HIV-1 infection—can prove invaluable.
An algorithm to guide the laboratory diagnosis of IM and heterophile-negative MLI is presented in the Figure, adapted from one published previously. Initial screening for a clinical picture consistent with IM should include heterophile antibody testing. If positive, this is highly suggestive of EBV-induced IM, but does not rule out the possibility of other infections, including HIV-1. If negative, a complete blood count (CBC) with automated differential may be helpful. Marked lymphocytosis (over 50% of all leukocytes) with atypical cells comprising at least 10% of all leukocytes constitutes Hoagland’s criteria for atypical lymphocytosis, suggesting heterophile-negative EBV-induced IM. Specific serologies for antibodies against EBV’s capsid (VCA) should be sent for confirmation. If the anti-VCA IgM and IgG assays are negative, request serologic testing for the 2 other main viral etiologies of MLI: CMV and HHV-6. Negative results should prompt a reassessment of the patient’s symptoms and history, with thought given to other less common diagnoses and appropriate testing.

**SUMMARY**

When a patient presenting with pharyngitis, lymphadenopathy, and fever has negative results on both HetAb and EBV-specific serologic tests, the clinician is faced with a diagnostic challenge. Consideration must be given to the many potential causes of heterophile-negative mononucleosis-like illness, with confirmatory testing driven by a careful appraisal of the patient’s clinical course, history of exposures and risks factors, and physical examination.

**ACKNOWLEDGMENTS**

We thank Penelope Dennehy, MD, Staci Fischer, MD, and Edward Wing, MD for their thoughtful review of the manuscript.

**References**

Incidence and Clinical Spectrum of Thiazide-associated Hypercalcemia

Robert A. Wermers, MD,a Ann E. Kearns, MD,a Gregory D. Jenkins, MS,b L. Joseph Melton, III, MDa,c

aDivision of Endocrinology, Department of Medicine, and bDivisions of Biostatistics and cEpidemiology, Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minn.

ABSTRACT

PURPOSE: The study determines the incidence of thiazide-associated hypercalcemia and clarifies its clinical features and natural history.

METHODS: In a population-based descriptive study, Olmsted County, Minn, residents with thiazide-associated hypercalcemia were identified through the Rochester Epidemiology Project and the Mayo Clinic Laboratory Information System. Changes in incidence rates were evaluated by Poisson regression.

RESULTS: Seventy-two Olmsted County residents (68 women and 4 men; mean age, 64 years) with thiazide-associated hypercalcemia first recognized in 1992 to 2001 were identified. The overall annual age- and sex-adjusted (to 2000 US whites) incidence was 7.7 (95% confidence interval [CI], 5.9-9.5) per 100,000. There was an increase in incidence after 1996, peaking at 16.3 (95% CI, 8.3-24.3) per 100,000 in 1998. The highest rate was 55.3 per 100,000 in 70- to 79-year-old women. Hypercalcemia was identified a mean of 6.7 years after thiazide initiation, and the average highest serum calcium was 10.7 ± 0.3 mg/dL with serum parathyroid hormone (obtained in 53 patients) of 4.8 ± 2.7 pmol/L. Of 33 patients who discontinued the thiazide, 21 (64%) had persistent hypercalcemia. Patients subsequently diagnosed with primary hyperparathyroidism had the highest average serum calcium and parathyroid hormone levels of 11.0 ± 0.3 mg/dL and 6.3 ± 2.4 pmol/L, respectively.

CONCLUSION: The persistence of hypercalcemia in patients discontinuing thiazides, and similarities in the clinical spectrum, suggest that underlying primary hyperparathyroidism is common in patients who develop hypercalcemia while taking thiazide diuretics. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Epidemiology; Hypercalcemia; Hyperparathyroidism; Incidence; Thiazide diuretic; Trends

Hypercalcemia associated with thiazide diuretic use is a well-recognized clinical entity.1 Mean 24-hour plasma calcium concentrations are increased with thiazide use, but mean 24-hour plasma parathyroid hormone levels remain unchanged in subjects with normal baseline parathyroid hormone levels and no evidence of hypercalciuria.2 Thiazides have several metabolic effects that may contribute to increased calcium levels. A reduction in urine calcium excretion is the most likely explanation, but a metabolic alkalosis associated with diuretic use also could cause an elevation in total serum calcium through a pH-dependent increase in protein-bound calcium. Although plasma 1,25(OH)2D levels are unchanged, increased intestinal calcium absorption in response to thiazide treatment has been noted and could also contribute to an increase in serum calcium. A final factor that may lead to the development of hypercalcemia is hemoconcentration associated with diuresis.10

Despite the well-known effect of thiazides increasing serum calcium levels, the incidence of thiazide-associated hypercalcemia has never been reported. Furthermore, prior
prevalence studies were performed before the introduction of automated serum calcium measurements. The only available data are from the early 1970s in Sweden where, in a health screen, 1034 of 15,903 persons between 20 and 63 years of age (66% women) were taking thiazides; among the thiazide-treated subjects, 20 (1.9%) were found to have hypercalcemia. The prevalence of hypercalcemia in this group was greater than that in the entire population (0.6%). Stenstrom and Heedman estimated the overall prevalence of hypercalcemia to be 0.1% to 0.2%, with a prevalence of 0.4% in thiazide-treated subjects.

The primary aim of this study was to determine the incidence of thiazide-associated hypercalcemia in the era of routine serum calcium measurement. In addition, we sought to clarify the clinical characteristics and natural history of thiazide-associated hypercalcemia in the general population. Given the demonstrated benefits of thiazide diuretics and their status as preferred first-step agents in the treatment of hypertension, we also wanted to provide timely clinical guidance in the evaluation and management of this disorder.

**CLINICAL SIGNIFICANCE**

- The annual incidence of thiazide-associated hypercalcemia was 7.7 per 100,000, with an increasing trend after 1996.
- Thiazide-associated hypercalcemia is often discovered several years after thiazide initiation.
- The persistence of hypercalcemia following discontinuation of thiazides suggests that underlying primary hyperparathyroidism is common in patients who develop hypercalcemia while taking thiazide diuretics.

**METHODS**

Population-based research is feasible in Olmsted County, Minn, because medical care is essentially self-contained within this community of approximately 124,000 residents. The area has relatively few providers, and 90% of the population is white. Most endocrinologic care is provided by the Mayo Clinic, which has maintained a common medical record with its 2 hospitals (St Marys and Rochester Methodist) for more than 100 years. The diagnoses and surgical procedures recorded in these records are indexed, as are the medical records of other providers who serve the local population. By using this unique record system (the Rochester Epidemiology Project), we identified all Olmsted County residents who were diagnosed with hypercalcemia between 1992 and 2001. We also identified all patients with primary hyperparathyroidism as described elsewhere. The following diagnostic rubrics were searched through 2003 (to allow patients in the process of being examined to be included in the diagnostic index): hyperparathyroidism (International Classification of Diseases, Ninth Revision [ICD-9 code, 252.0], parathyroid adenoma (ICD-9 code, 227.1), osteitis fibrosa cystica (ICD 9-code, 588.8), malignant hypercalcemia/ectopic hormone secretion (ICD-9 code, 259.3), and hypercalcemia not otherwise specified (ICD-9 code, 275.4). In addition, all Olmsted County residents with serum calcium levels exceeding 10.1 mg/dL at least twice, between 1992 and 2001, were identified directly from Mayo’s Laboratory Information System.

Patients were accepted as having thiazide-associated hypercalcemia if they met the following criteria: sustained hypercalcemia (serum calcium > 10.1 mg/dL) documented on 2 or more measurements with concomitant thiazide diuretic use for which no other cause (eg, pathologically or biochemically proven primary hyperparathyroidism before initiation of the thiazide diuretic, malignancy, family history of familial benign hypercalcemia, creatinine level > 2 mg/dL, or lithium therapy) was identified. The methods used at the Mayo Clinic to measure serum calcium levels changed over time; however, the normal range (8.9-10.1 mg/dL) remained the same because the instrumentation was calibrated not against the manufacturer’s standard but against atomic absorption spectrophotometry (according to certified references from the National Bureau of Standards). The date of diagnosis of thiazide-induced hypercalcemia was the date of the first elevated calcium level while taking a thiazide diuretic. Patients with thiazide-associated hypercalcemia who subsequently had biochemically proven primary hyperparathyroidism must have met the inclusion criteria outlined in our previous studies. For each case identified, the complete (inpatient and outpatient) medical record in the community was reviewed by 1 of the investigators (R.A.W.). Mayo Clinic records contain the details of every inpatient hospitalization at its 2 hospitals, every outpatient office or clinic visit, all emergency department and nursing home care, and all laboratory, radiographic, and pathology reports, including autopsies. This information was supplemented by that available from the other providers of care to local residents, most notably the Olmsted Medical Center.

Incidence rates were calculated as of the date of the initial elevated serum calcium level after initiation of the thiazide. The denominator age- and sex-specific person-years for the entire population of Olmsted County were...
estimated from decennial census data with interpolation between census years. Standard errors and 95% confidence intervals were calculated for the rates, assuming that they follow a Poisson distribution. Incidence rates were directly age- and/or age- and sex-adjusted to the population structure of white persons in the United States in 2000. Poisson regression was used to compare male and female incidence rates adjusted for age. The cumulative probability of primary hyperparathyroidism diagnosis after thiazide discontinuation was calculated using the Kaplan-Meier method.

RESULTS
We identified 72 Olmsted County residents with thiazide-associated hypercalcemia (68 women and 4 men) during the 10-year study period, 1992 to 2001. The overall annual age- and sex-adjusted incidence was 7.7 (95% confidence interval [CI], 5.9-9.5) per 100,000 (Table 1). The incidence of thiazide-associated hypercalcemia increased after 1996, with a peak incidence of 16.3 (95% CI, 8.3-24.3) per 100,000 in 1998 (Table 2). The age-adjusted incidence was higher in women (13.5 per 100,000 person-years; 95% CI, 10.3-16.8) than in men (0.9 per 100,000 person-years; 95% CI, 0.0-1.8; \( P < 0.001 \)). The highest incidence was 55.3 per 100,000 person-years in 70- to 79-year-old women.

The mean age at diagnosis was 64 ± 11 years, and women comprised the majority of cases (94%) (Table 3). Laboratory results indicated mild hypercalcemia, with a mean highest serum calcium on thiazides of 10.7 ± 0.3 mg/dL (range, 10.2-11.5 mg/dL). Before initiation of thiazides, the mean serum calcium was 9.7 ± 0.4 mg/dL as measured in 57 subjects. Of those without a serum calcium level before thiazide initiation, 10 patients (67%) had a normal serum calcium measurement before the detection of hypercalcemia. The elevated serum calcium level was identified on average 6.0 ± 7.2 years after the initiation of thiazide treatment (range, 14 days to 27 years). Serum parathyroid hormone was measured in 53 patients after the identification of hypercalcemia and averaged 4.8 ± 2.7 pmol/L (range, 0.4-13 pmol/L). The serum parathyroid hormone was less than 2.1 pmol/L in 7 subjects (13.2%), 2.2 to 5.2 pmol/L in 29 subjects (54.7%), and more than 5.2 pmol/L in 17 subjects (32.1%). None of the patients with a suppressed parathyroid hormone level had an identifiable secondary cause of their hypercalcemia, and the onset of hypercalcemia in all of these patients was more than 1 year after thiazide initiation. Patients without a serum parathyroid hormone measurement had less severe hypercalcemia (10.46 ± 0.19) but were otherwise similar to the overall cohort. The most common reason for thiazide initiation was hypertension (94%); edema (3%) and hypercalciuria/nephrolithiasis (3%) were the other rationales for its use.

### Table 1: Incidence of Thiazide-associated Hypercalcemia Among Olmsted County, Minn, Residents, 1992 to 2001, by Gender and Age Group

<table>
<thead>
<tr>
<th>Age Group (y)</th>
<th>Women</th>
<th>Rate* (95% CI)</th>
<th>Men</th>
<th>Rate* (95% CI)</th>
<th>Both Sexes</th>
<th>Rate* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30-39</td>
<td>1</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>40-49</td>
<td>5</td>
<td>5.5</td>
<td>1</td>
<td>1.2</td>
<td>6</td>
<td>3.4</td>
</tr>
<tr>
<td>50-59</td>
<td>21</td>
<td>35.4</td>
<td>1</td>
<td>1.8</td>
<td>22</td>
<td>19.0</td>
</tr>
<tr>
<td>60-69</td>
<td>18</td>
<td>45.5</td>
<td>1</td>
<td>2.8</td>
<td>19</td>
<td>25.1</td>
</tr>
<tr>
<td>70-79</td>
<td>17</td>
<td>55.3</td>
<td>1</td>
<td>4.4</td>
<td>18</td>
<td>33.8</td>
</tr>
<tr>
<td>80-89</td>
<td>5</td>
<td>25.0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>17.0</td>
</tr>
<tr>
<td>≥90</td>
<td>1</td>
<td>18.1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>14.6</td>
</tr>
<tr>
<td>Total</td>
<td>13.5 (10.3-16.8)†</td>
<td>0.9 (0.0-1.8)†</td>
<td>7.7 (5.9-9.5)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval.
*Incidence per 100,000 person-years.
†Incidence per 100,000 person-years directly age-adjusted to the US white population in 2000.
‡Incidence per 100,000 person-years directly age- and sex-adjusted to the US white population in 2000.

### Table 2: Trends in the Incidence of Thiazide-associated Hypercalcemia Among Olmsted County, Minn, Residents, 1992 to 2001, by Year

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Rate* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>4</td>
<td>4.9 (0.1-9.8)</td>
</tr>
<tr>
<td>1993</td>
<td>3</td>
<td>3.6 (0.7-7.8)</td>
</tr>
<tr>
<td>1994</td>
<td>6</td>
<td>7.1 (1.4-12.8)</td>
</tr>
<tr>
<td>1995</td>
<td>4</td>
<td>4.6 (0.1-9.0)</td>
</tr>
<tr>
<td>1996</td>
<td>3</td>
<td>3.0 (0.0-6.5)</td>
</tr>
<tr>
<td>1997</td>
<td>8</td>
<td>8.6 (2.6-14.6)</td>
</tr>
<tr>
<td>1998</td>
<td>16</td>
<td>16.3 (8.3-24.3)</td>
</tr>
<tr>
<td>1999</td>
<td>12</td>
<td>12.3 (5.3-19.2)</td>
</tr>
<tr>
<td>2000</td>
<td>6</td>
<td>5.8 (1.1-10.5)</td>
</tr>
<tr>
<td>2001</td>
<td>10</td>
<td>9.5 (3.5-15.4)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
*Incidence per 100,000 person-years directly age- and sex-adjusted to the US white population in 2000.
The thiazide was abruptly discontinued in 33 patients (in 12.5% [95% CI, 4.5-19.8] within 1 year, 25.1% [95% CI, 14.3-34.4] within 3 years, and 34.6% [95% CI, 22.2-45.1] within 5 years after initiation of treatment) and was then reinitiated in 2 patients (Figure 1). Serum calcium stayed persistently normal in 7 patients discontinuing thiazides, with a mean last serum calcium measurement 5.4 years after the thiazide was discontinued. Twenty-one patients (64%) continued to have hypercalcemia despite discontinuing the thiazide, 18 of whom were formally diagnosed with primary hyperparathyroidism (39.7% [95% CI, 19.2-55.2] within 1 year, 48.3% [95% CI, 25.8-68.4] within 3 years, and 65.5% [95% CI, 32.5-83.7] within 5 years after discontinuation) (Figure 2). In patients with continued hypercalcemia after discontinuing the thiazide, 5 patients had initial normalization of their serum calcium level, followed by recurrent hypercalcemia an average of 3.1 ± 1.2 years later. Five patients who discontinued thiazides did not have their serum calcium level measured after discontinuation.

Thirty-seven subjects (51%) continued the thiazide and did not have parathyroid surgery; 2 subjects had parathyroid surgery without discontinuing the thiazide. Serum calcium levels were measured in all patients after meeting the inclusion criteria for thiazide-associated hypercalcemia. Their last measured mean serum calcium level was 9.9 ± 0.4 mg/dL (range, 8.8-11.1 mg/dL) an average of 5.7 ± 2.1 years (range, 2.6-11.1 years) after detection of hypercalcemia, with continued hypercalcemia on the last measurement in 11 subjects (30%). In the 26 patients with a last measured serum calcium level in the normal range, 5 (19%) had a single measurement, 7 (27%) had persistently normal calcium levels, and 14 (54%) had intermittent hypercalcemia. When compared with those in whom the thiazide was discontinued, patients remaining on thiazides had lower mean serum calcium and parathyroid hormone levels (Table 4).

Primary hyperparathyroidism was diagnosed in 20 patients with thiazide-associated hypercalcemia. Of the patients with primary hyperparathyroidism, 10 (50%) had pathologic confirmation, 7 (35%) had an inappropriate parathyroid hormone in the setting of hypercalcemia, and 3 (15%) had persistent hypercalcemia for 1 year or more after discontinuing the thiazide. In patients diagnosed with primary hyperparathyroidism, 18 (90%) were asymptomatic. The 2 patients with symptomatic disease had kidney stones. The mean age at onset of hypercalcemia in the patients diagnosed with primary hyperparathyroidism was 66 years, and 19 (95%) were women (Table 3). The mean maximum serum calcium in this subset of patients was 11.0 ± 0.3 mg/dL, with a mean parathyroid hormone level of 6.3 ± 2.4 pmol/L (range, 3.4-12.0 pmol/L) at the time closest to the diagnosis of primary hyperparathyroidism. The mean time to identification of hypercalcemia after initiation of the thiazide in patients diagnosed with primary hyperparathyroidism was 7.3 years.

---

### Table 3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients Mean ± SD, or n (%)</th>
<th>Primary Hyperparathyroidism Subset Mean ± SD, or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>68 (94.4)</td>
<td>19 (95.0)</td>
</tr>
<tr>
<td>Age at onset of hypercalcemia, y</td>
<td>63.9 ± 11.3</td>
<td>66.2 ± 11.2</td>
</tr>
<tr>
<td>Serum calcium before thiazide use, mg/dL</td>
<td>9.7 ± 0.4</td>
<td>9.7 ± 0.5</td>
</tr>
<tr>
<td>Maximum serum calcium on thiazides, mg/dL</td>
<td>10.7 ± 0.3</td>
<td>11.0 ± 0.4</td>
</tr>
<tr>
<td>Serum parathyroid hormone, pmol/L</td>
<td>4.8 ± 2.7</td>
<td>6.3 ± 4.4</td>
</tr>
<tr>
<td>Years from thiazide start to hypercalcemia</td>
<td>6.0 ± 7.2</td>
<td>7.3 ± 8.5</td>
</tr>
<tr>
<td>Reason for thiazide use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>68 (94.4)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Edema</td>
<td>2 (2.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypercalciuria/nephrolithias</td>
<td>2 (2.8)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

<sup>SD = standard deviation.</sup>
DISCUSSION
In this study, the first to estimate the incidence of thiazide-associated hypercalcemia, we found an overall age- and sex-adjusted incidence of 7.7 per 100,000 person-years in our community. In general, the incidence increased after 1996, with a peak of 16.3 per 100,000 in 1998. One potential explanation for this trend could be the increased use of thiazides since the ALLHAT trial.20 However, because of significant changes in our prescription ordering system during the period of interest, we were unable to confidently quantify thiazide prescription trends at our institution.

Factors other than thiazides may be important in the development of hypercalcemia. Patients with a clear cause for hypercalcemia were excluded from our results. Thus, the primary diagnostic considerations in this setting would be primary hyperparathyroidism or the thiazide itself. To distinguish between these 2 conditions, it is often necessary to discontinue the thiazide for up to 3 months, because hypercalcemia has been reported to resolve once thiazides are discontinued. However, Christianson and colleagues11 reported that hypercalcemia resolved in only 5 of 20 subjects 1 to 3 months after thiazide discontinuation and that 14 of the 15 subjects with persistent hypercalcemia had pathologically confirmed primary hyperparathyroidism. This is consistent with our finding that 64% of community patients identified with thiazide-associated hypercalcemia remained hypercalcemic after treatment was discontinued, suggesting another underlying cause, for example, primary hyperparathyroidism.

Indeed, the clinical characteristics of thiazide-associated hypercalcemia are similar to those seen for primary hyperparathyroidism in this population.16,17 The average age was 64 years and 94% were females in the thiazide cohort, and the average age was 56 years and 69% were women in the primary hyperparathyroidism cohort from the same period.17 The observed gender discrepancy suggests that postmenopausal women are predisposed to developing hypercalcemia while taking thiazides, but an additional factor may be that more women than men are taking thiazides for the treatment of hypertension.21 The mean maximum serum calcium level (10.7 mg/dL) in our subjects was identical to that seen in primary hyperparathyroidism.17 Furthermore, in subjects who remained on thiazides, the last serum calcium measurement was 9.9 mg/dL, suggesting a nonprogressive process as is often seen in mild primary hyperparathyroidism.22 Consistent with previous literature, complications were limited to 2 patients, both of whom were later diagnosed with primary hyperparathyroidism.16 Although patients diagnosed with primary hyperparathyroidism appeared to be similar to the overall group of patients with thiazide-associated hypercalcemia, on av-

Table 4  Clinical and Laboratory Spectrum of Thiazide-Associated Hypercalcemia Among Olmsted County, Minn, Residents, 1992 to 2001, Comparing Subsets Continuing and Discontinuing Thiazide

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Thiazide Discontinuation</th>
<th>Thiazide Continuation Without Parathyroid Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD, or n (%)</td>
<td>Mean ± SD, or n (%)</td>
</tr>
<tr>
<td>Female gender</td>
<td>30 (90.9)</td>
<td>36 (97.3)</td>
</tr>
<tr>
<td>Age at onset of hypercalcemia, y</td>
<td>67.48 ± 10.24</td>
<td>60.76 ± 11.03</td>
</tr>
<tr>
<td>Serum calcium before thiazide use, mg/dL</td>
<td>9.64 ± 0.37</td>
<td>9.71 ± 0.37</td>
</tr>
<tr>
<td>Maximum serum calcium on thiazides, mg/dL</td>
<td>10.80 ± 0.38</td>
<td>10.56 ± 0.20</td>
</tr>
<tr>
<td>Serum parathyroid hormone, pmol/L</td>
<td>5.38 ± 2.82</td>
<td>3.66 ± 1.83</td>
</tr>
<tr>
<td>Range, pmol/L</td>
<td>1.8-13</td>
<td>0.4-7.6</td>
</tr>
<tr>
<td>Not measured</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Parathyroid hormone ≤ 2.1 pmol/L</td>
<td>2 (7.1)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Parathyroid hormone 2.2-5.2 pmol/L</td>
<td>16 (57.1)</td>
<td>13 (56.5)</td>
</tr>
<tr>
<td>Parathyroid hormone &gt; 5.2 pmol/L</td>
<td>10 (35.7)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Years from thiazide start to hypercalcemia</td>
<td>7.92 ± 8.40</td>
<td>4.67 ± 6.01</td>
</tr>
<tr>
<td>Reason for thiazide use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Edema</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypercalciuria/nephrolithias</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

SD = standard deviation.
erage, they had higher maximum serum calcium (11.0 vs 10.7 mg/dL) and parathyroid hormone (6.3 vs 4.8 pmol/L) levels. It is also likely that several of the subjects remaining on thiazides with unsuppressed parathyroid hormone levels or continued hypercalcemia had underlying primary hyperparathyroidism.

The specific relationship between thiazide use and primary hyperparathyroidism is uncertain. Work from Pickleman and colleagues suggested that thiazide use induced enlargement of the parathyroid glands. Alternatively, the association may simply represent a chance association between 2 conditions (hypertension and primary hyperparathyroidism) that are more prevalent with increasing age. In addition, the renal tubular Na-Cl cotransporter has been suggested as a link between hypertension and calcium homeostasis. Specifically, higher urinary calcium excretion might unmask mild or normocalcemic primary hyperparathyroidism. Conversely, thiazide use theoretically could reduce parathyroid gland stimulation through renal and intestinal mechanisms and delay the development of primary hyperparathyroidism.

Our study has several limitations attributable to its design. We did not have prospective measurements of serum calcium in all patients taking thiazides, and serum calcium was not measured at specific time points before or after thiazide initiation. Also, we did not have routine measurements of serum albumin or a formal assessment of dietary calcium and vitamin D intake, all of which may influence serum calcium measurements. In addition, the population of Olmsted County is primarily white, limiting the application of study results to more ethnically diverse populations. Nonetheless, the results would be representative of typical patients encountered in clinical practice. Furthermore, our unique record system allowed comprehensive follow-up of all community medical care. A comparable prospective study to identify thiazide-associated hypercalcemia would require an estimated 3600 study subjects followed for at least 6 years.

The appropriate clinical management of patients with thiazide-associated hypercalcemia is poorly delineated. After confirmation of sustained hypercalcemia, a serum parathyroid hormone determination is useful in narrowing the diagnostic considerations. Although thiazides will often be discontinued to determine whether they are the cause of the hypercalcemia, hypercalcemia has been described as mild and nonprogressive, and often consists of a temporary elevation shortly after the onset of therapy. Our results are consistent with mild, asymptomatic, and nonprogressive disease. In patients without an easily identifiable cause of hypercalcemia who are taking thiazides and have an unsuppressed parathyroid hormone level, a reasonable strategy may be to follow guidelines for asymptomatic primary hyperparathyroidism. Although exacerbation of hypercalcemia is a concern if thiazides are continued, it seems that thiazides do not worsen hypercalcemia in patients who develop mild primary hyperparathyroidism. However, there are case reports of severe hypercalcemia in patients with primary hyperparathyroidism who are initiated on thiazide diuretics. This study did not address the issue of starting thiazides in patients with known primary hyperparathyroidism.

CONCLUSION

The overall age- and sex-adjusted annual incidence of thiazide-associated hypercalcemia in Olmsted County from 1992 to 2001 was estimated at 7.7 per 100,000 with an increasing trend since 1996 for unclear reasons. The typical patients were women with mild, uncomplicated, and nonprogressive hypercalcemia that was discovered approximately 6 years after thiazide initiation. Excluding readily identifiable causes of hypercalcemia, we estimate that approximately two thirds of the patients with thiazide-associated hypercalcemia have underlying primary hyperparathyroidism. Because there is increasing use of thiazides as first-line antihypertensive agents, combined with an aging population at increased risk for parathyroid disease, a further increase in the incidence of thiazide-associated hypercalcemia might be expected. It will be important to monitor long-term trends in this condition and to consider prospective studies to further characterize its long-term natural history.

ACKNOWLEDGMENT

The authors thank Mrs Mary Roberts for assistance in preparing the article.

References


Marinol-Induced Gynecomastia: A Case Report

To the Editor:

The relationship between marijuana use and gynecomastia remains controversial. The association was first published by Harmon and Aliapoulios. Several publications confirming this relationship followed. Patients using marijuana were noted to have both gynecomastia and an increase in the human chorionic gonadotropin levels. The discontinuation of marijuana use resulted in resolution of the gynecomastia and normalization of the human chorionic gonadotropin levels. The present report describes a patient with gynecomastia induced by dronabinol (Marinol, Solvay Pharmaceuticals Inc, Marietta, Ga).

CASE REPORT

The patient presented is a 48-year-old man with a 2-month history of a right retroareolar breast mass. The mass appeared approximately 30 days after he began taking 5 mg of dronabinol (Marinol) per day for recurrent, severe nausea secondary to an extensive gastrointestinal history. On physical examination, the mass was mobile and tender to palpation without concerning lymphadenopathy. There was no hepatosplenomegaly on abdominal examination, and no testicular masses. Mammogram and ultrasound of the mass revealed a small, dense focus of parenchyma immediately retroareolar without suspicious microcalcifications. Fine-needle aspiration of the mass demonstrated cellularity consistent with gynecomastia. Serum levels of testosterone, prolactin, and thyroxine were within normal limits, as well as liver function test results. Pertinent to his medical history, the patient had a benign contralateral breast mass consistent with gynecomastia removed nearly 20 years ago. This followed a history of testicular cancer treated with unilateral orchietomy.

DISCUSSION

This case report demonstrates an observed relationship between gynecomastia and dronabinol (Marinol) use. This relationship has not been mentioned in the literature; however, the relationship between marijuana use and gynecomastia has been documented. Marijuana has been found to be associated with hyperprolactinemia and gynecomastia. However, another study of the relationship between gynecomastia and cannabis smoking among men showed no association between the two. The concentration of δ-9-tetrahydrocannabinol consumed by patients in previous studies was not quantified. This makes it difficult to know the dosage at which patients using dronabinol (Marinol) may experience gynecomastia. Two further studies published conflicting results concerning the effect of marijuana use on testosterone levels in men. One study found a dose-related effect of marijuana on plasma levels of testosterone. However, they were unable to confirm the relationship between cannabis and gynecomastia. The other study found no relationship between marijuana use and testosterone levels in men. These studies demonstrate the need for further research to elucidate the role of δ-9-tetrahydrocannabinol in gynecomastia.

When presented with a patient with a breast mass and a history of dronabinol (Marinol) use, physicians should be aware of the possible diagnosis of gynecomastia.

Rebekah C. Allen, MS, Anne Marie Wallace, MD, Melanie Royce, MD, PhD

Department of Surgery, University of New Mexico, Albuquerque

References

Sarcoidosis Manifesting as a Periorbital Purplish Rash

To the Editor:

Sarcoidosis is a multisystemic non-caseating granulomatous disease that occurs in people of all races and ages. Cutaneous involvement in sarcoidosis is often present at the onset of the disease and the frequency is approximately 25%.

CASE REPORT

A previously healthy 66-year-old Japanese man presented with a 6-month history of pruritic puffy erythematous eyelids. He was diagnosed with allergic blepharitis by an ophthalmologist and subsequently a dermatologist, and treated with antihistamines and nonsteroidal anti-inflammatory drugs. Physical examination showed a periorbital purplish erythema with a notable bilateral swelling of his upper eyelids. A skin biopsy specimen taken from the upper eyelid revealed that there were multiple non-caseating granulomas composed of epithelioid cells in the dermis (Figure). A histological diagnosis of sarcoidosis was made. He had no other skin lesions or superficial lymphadenopathy. A computed tomography examination of the chest showed right-sided paratracheal lymphadenopathy with small nodules in both lower lobes of the lung. Gallium scanning test showed an abnormal uptake of the bilateral hilar lymph nodes. These results supported the notion that he was suffering from sarcoidosis. Laboratory data including serum angiotensin-converting enzyme and calcium were within normal limits. Pulmonary function studies were normal. An ophthalmologic consultation determined that he had no evidence of uveitis or presence of sarcoideal nodules in the orbit. His periorbital skin lesions soon improved after topical treatment with potent corticosteroids. His pulmonary and nodal lesions have remained static, and he is seen regularly.

DISCUSSION

We believe the initial diagnosis of allergic blepharitis is not unsuitable for a clinical diagnosis in the present erythema. The accompanying pruritus supported this diagnosis. Another important clinical differential diagnosis might be a heliotrope rash. Persistent violaceous erythema with edema of the periorbital skin strongly suggests a heliotrope rash, which is a pathognomonic cutaneous feature of dermatomyositis. However, search of the literature has failed to disclose examples of cutaneous sarcoidosis presenting as periorbital erythema. The present rash was, thus, an unusual manifestation of sarcoidosis.

Cutaneous sarcoidosis has been classically classified into the following groups: maculopapular eruptions, plaques, subcutaneous nodules, infiltration of old scars, and lupus pernio. Subcutaneous sarcoideal nodules tend to spontaneously remit, but lupus pernio is more persistent. Clinical investigations, including chest radiography, gallium scanning test, pulmonary function tests, and routine blood analysis—particularly serum angiotensin-converting enzyme and calcium level—should be undertaken in all patients with cutaneous sarcoideal lesions, even in cases with minimal skin involvement. None of these findings are specific for sarcoidosis, and the most important single criterion for the
diagnosis is the finding of typical granulomas histologically. However, these investigations may confirm the diagnosis of sarcoidosis and may be helpful in the assessment for systemic involvements and monitoring the activity of the disease. Cutaneous sarcoidal lesions most effectively improve with topical or oral corticosteroid therapies, and methotrexate has been recommended for use as a corticosteroid-sparing agent in severe cases.

It has been reported that physicians often have encountered difficulties in making a diagnosis of sarcoidosis, so that the diagnosis of sarcoidosis was delayed from the onset of symptoms. Conversely, sarcoidosis is more easily diagnosed when the skin manifestations are the first symptoms noticed by the patient or after physical examination. However, this does not necessarily mean that it is easy to recognize a skin lesion as typical sarcoidosis. Cutaneous involvement can manifest itself in an unusual form, as in the present case. This case reminds clinicians that if an eruption looks suspicious, an early skin biopsy should be performed. This step could make the correct diagnosis of sarcoidosis significantly quicker.

References
Alcohol and Gout

To the Editor:

Zhang and colleagues recommend that “subjects with gout should avoid drinking alcoholic beverages entirely, despite the salutary effects of light-to-moderate alcohol intake on other diseases.”

In the general population, the overall health benefits of moderate drinking (1-2 drinks/day for men and ≤1 drink/day for women) likely outweigh the risks, as permitted by dietary guidelines from the United States Department of Agriculture (www.healthierus.gov/dietaryguidelines) and the American Heart Association, and a recent food pyramid (http://www.hsph.harvard.edu/nutritionsource/pyramids.html). More than 60 prospective studies have consistently indicated that moderate alcoholic consumption is associated with a 25% to 40% reduced risk for coronary heart disease (CHD). Also, prospective studies suggest a similar protective effect against other cardiovascular diseases and deaths. These benefits are particularly relevant to middle-aged men, the demographic in whom gout occurs most often. Furthermore, the benefits may be more relevant to gout patients, who often suffer cardiovascular comorbidities and are at an increased risk for CHD.

We note that the reported risk estimates in Zhang et al’s study were derived from a relatively small number of patients who experienced gout attack(s) during the study (n=144). Furthermore, the observed associations are open to potentially important recall bias given the fact that the alcohol-gout link is well-known. Nevertheless, at the relevant moderate intake level (1-2 drinks/day), no individual alcoholic beverages suggested an increased risk of gout (odds ratio [OR] 1.1 for beer, 1.2 for wine, and 0.8 for spirits, all P-values >.05). Furthermore, the OR for wine, in particular, remained similar even at the level of 3-4 drinks/day (OR 0.9), although ORs for beer and spirits increased (1.6 and 2.0, respectively). These data agree with the null association with moderate wine drinking (and positive associations with beer and spirits) found in our prospective study of incident gout based on 730 cases in 47,150 men. This is further supported by the null association between moderate wine drinking and serum urate levels.

Thus, the available data do not support a strict recommendation to forbid all alcohol intake at light-to-moderate levels among gout patients. Rather, moderate wine drinking (perhaps not beer or spirits) may be allowed to help achieve other important health benefits, as above. Future studies specifically powered for the effect among gout patients would help clarify the issue further. Finally, as in any dietary/lifestyle guideline, this recommendation should carefully take into account other related benefits and risks to maximize the overall health outcomes on a long-term as well as a short-term basis.

Hyon K. Choi, MD, DrPH
Rheumatology Division
Arthritis Research Centre of Canada
Department of Medicine
Vancouver General Hospital
University of British Columbia
Vancouver, Canada
Channing Laboratory
Boston, Mass.

Gary Curhan, MD, ScD
Channing Laboratory
Boston, Mass.
Renal Division
Department of Medicine
Brigham and Women’s Hospital
Harvard Medical School
Boston, Mass.


References

The Reply:

In their letter to the Editor, Choi et al voiced their concern regarding our recommendation that “subjects with gout should avoid drinking alcoholic beverages entirely, despite the salutary effects of light-to-moderate alcohol intake on other diseases.” They commented that no individual alcoholic beverages at the relevant moderate intake levels (1-2 drinks/day) in our study suggested an increased risk of gout attacks. They suggest that (among patients with gout) moderate wine drinking (perhaps not beer or spirits) may be allowed to help achieve other important health benefits.

In their letter, Choi et al did not comment on the strong dose-response relationship between the total amount of alcohol (wine, beer, and spirits) and risk of incident and recurrent gout attacks. We reported that the odds ratios for recurrent gout attacks were 1.4, 1.6, 2.7, and 3.1 for consumption of 1 to 2, 3 to 4, 5 to 6, and 7 or more alcoholic drinks over 24 hours before a gout attack, respectively, compared with no alcohol consumption (P for trend < .023).1 Choi et al also reported that the relative risks of incident gout attack were 1.32, 1.49, 1.96, and 2.53 for subjects consuming 10.0 to 14.9, 15.0 to 29.9, 30.0 to 49.9, and ≥50 g per day of alcohol, respectively, compared with those who did not drink alcohol (P for trend < .001) among participants in the Health Professionals Follow-up Study.2 Both studies demonstrated that light-to-moderate alcohol consumption increases the risk for incident and recurrent gout attacks, and the magnitude of effect was similar.

Many patients with gout also have or are at higher risk of other diseases, including cardiovascular disease.3 Although randomized clinical trial data are lacking, numerous epidemiologic studies have shown that regular moderate alcohol consumption, irrespective of beverage type, is associated with a lower risk of an initial or of recurrent cardiovascular disease.4 Similarly, other healthy lifestyle factors, such as abstinence from smoking, regular physical exercise, and maintenance of optimal body weight, also play important roles in reducing the risk of cardiovascular and many other diseases.5 Furthermore, for those who are at higher risk of cardiovascular disease, chemoprevention, such as statin use, may also provide a significant clinical benefit.5 Thus, for subjects with gout, various measures other than alcohol are available to reduce their risk of cardiovascular disease without necessarily increasing their risk for painful gout attacks.

Compared with the totality of evidence on an association between total amount of alcohol consumption and gout attacks, to date, there are a paucity of data suggesting that risk of either incident or recurrent gout attack vary according to specific alcoholic beverages. Additional studies with adequate statistical power are needed to test this hypothesis. Thus, to reduce the risk of recurrent gout attacks, the best advice for the patients with gout is to avoid alcohol intake.6

Yuqing Zhang, DSc
Tuhina Neogi, MD
David J. Hunter, MD, PhD
Clinical Epidemiology Research and Training Unit
Department of Medicine
Boston University School of Medicine
Boston, Mass
doi:10.1016/j.amjmed.2006.11.021

References
LETTER

Functional Status in Chronic Obstructive Pulmonary Disease

To the Editor:

In a recent article, Reardon and coworkers\(^1\) reviewed the impact of exertional dyspnea on functional status and quality of life in patients with chronic obstructive pulmonary disease (COPD). They also reviewed the methods to measure functional status and quality of life, and proposed a brief evaluation based on a simple scoring of overall dyspnea together with an unstructured functional status evaluation covering 1 or more activity of daily living, such as showering, leaving the house, or a particular social activity.

By using main components analysis, we recently reported that elderly hospitalized patients with COPD have a distinctive clustering of basic and instrumental activities of daily living (IADL) that are clearly different from those observed in elderly patients with other chronic conditions, such as diabetes mellitus and congestive heart failure. The hierarchy of IADL that characterizes COPD reveals 2 factors: the expression of IADL related to outdoor mobility and selected, highly demanding IADL requiring both physical and mental capabilities, such as managing money, taking medicines, and traveling. Both factors are associated with a longer hospital stay, that is, a greater need of care, whereas only the latter is associated with a greater prevalence of cognitive impairment.\(^2\)

Although difficulty in moving outdoors is a distinctive and established feature of COPD-related disability,\(^1,3\) dependency in IADL requiring good cognitive function would remain concealed using the brief clinical assessment proposed by Reardon and coworkers.\(^1\) For example, dependency in taking medicine because of memory impairment may have a relevant impact on the burden of disease. Indeed, compliance with both drugs and oxygen therapy is poor in patients with COPD with cognitive impairment, and poor compliance is a risk factor for acute exacerbations.\(^4,5\)

Therefore, a brief clinical evaluation of functional status in patients with COPD should take into account not only the ability to perform physically demanding activities, such as showering or leaving the house, but also the ability to perform cognitively demanding IADL.

Andrea Corsonello, MD
Fondazione San Raffaele
Cittadella della Carità
Taranto, Italy

Istituto Nazionale di Ricovero e Cura per Anziani Cosenza, Italy

Claudio Pedone, MD
Cattedra di Geriatria
Università Campus BioMedico
Rome, Italy

Raffaele Antonelli Incalzi, MD
Fondazione San Raffaele
Cittadella della Carità
Taranto, Italy

Cattedra di Geriatria
Università Campus BioMedico
Rome, Italy

doi:10.1016/j.amjmed.2006.09.023

References


The Reply:

Our review focused on the importance of dyspnea and activity limitation in the quality of life of individuals with chronic obstructive pulmonary disease. In particular, we emphasized the inverse relationship between exertional dyspnea and physical activity limitation in this disease. Corsonello and colleagues describe their research indicating that impairments in cognitive function are also potentially important in the functional status of hospitalized patients with chronic obstructive pulmonary disease. Our recommendation to the clinician of including a few brief questions on physical activity limitation in addition to dyspnea evaluation was not meant to be exhaustive.

Richard ZuWallack, MD
St Francis Hospital
Pulmonary
Hartford, Conn

doi:10.1016/j.amjmed.2006.10.012
LETTER

Broadening the Differential Diagnosis from a Different Perspective

To the Editor:

Although not included in the disease associations mentioned by the author, celiac disease may be associated with inflammatory bowel disease (IBD) to a degree that is perhaps greater than can be ascribed to pure chance. In the event of such an association, there is the potential for coexisting celiac disease to be overlooked or for one of the presenting symptoms, such as diarrhea, to be misattributed to celiac disease or IBD. Misattribution also can occur when the presenting symptom is abdominal pain, given the fact that this is a symptom common to both celiac disease and Crohn’s disease, and, for the same reason, in the event of a presentation characterized by hematinic deficiencies.

Supporting evidence for the association of celiac disease and IBD comes from a study that compared the prevalence of IBD in a cohort of 455 patients with celiac disease with the prevalence of IBD in the US population. This yielded an age- and sex-adjusted prevalence ratio of 8.49 (95% confidence interval, 3.53-20.42) for Crohn’s disease and 3.56 (95% confidence interval, 1.48-8.56) for ulcerative colitis. Among first-degree relatives of patients with celiac disease, there also seems to be an increased risk of IBD; the relative risk of ulcerative colitis, in particular, is 5 times higher in these patients than for the general population.

The association also has prognostic implications, as shown in a study in which the coexistence of celiac disease and IBD conferred a higher mortality risk (attributable to small bowel cancer and non-Hodgkin lymphoma, respectively) in those with the association than in those without the association.

Oscar M. Jolobe, MRCP(UK) (retired geriatrician)
Manchester Medical Society
Manchester, United Kingdom

doi:10.1016/j.amjmed.2006.09.026

References
Effective Detection of Celiac Disease Using Salivary Anti-transglutaminase

To the Editor:

Celiac disease (CD) was previously considered to be a rare pediatric disease caused by gluten intolerance and presenting most often with diarrhea, steatorrhea, and weight loss. Recently, however, different trends in the presentation of CD have been reported. Most cases are diagnosed in adults presenting no diarrhea, but rather other various clinical disorders, such as iron-deficiency anemia, osteoporosis, neurologic or psychiatric symptoms, abdominal pain, and even constipation. In the general population, several serologic screening studies have demonstrated a prevalence of approximately 0.5% to 1%.

Detection of serum anti-human transglutaminase (TG) immunoglobulin-A antibodies is recognized as the most reliable serologic screening test. For less-invasive screening tests, several attempts have been made to detect these antibodies in saliva. Unfortunately, the only successful test cannot be used on a large scale in most clinical diagnostic laboratories because it is a fluid-phase radioimmunoassay using radio-labeled TG. We report the results obtained with a commercial solid-phase enzyme-linked immunosorbent assay test (Celikey, Sweden Diagnostics, Freiburg, Germany) demonstrating an excellent discrimination between saliva from subjects with and without CD. Saliva samples were collected with an Omnisal device (Saliva Diagnostic System, London, UK) and treated (20 minutes at room temperature) with N-acetyl-cysteine to achieve a final concentration of 0.63 mg N-acetyl-cysteine per milliliter of saliva. The samples were then tested without further dilution with the Celikey following the manufacturer’s instructions for serum samples. The positivity threshold for salivary samples was determined by comparing the results for subjects with CD with those obtained for healthy controls and was fixed at 4 U/mL. We tested the saliva collected from 20 untreated patients with CD, 38 healthy control subjects, and 22 patients with clinical symptoms compatible with a diagnosis of CD but who finally did not meet the criteria for diagnosis (disease controls). Receiver operating curve analysis of these data gives a sensitivity of 90% and a specificity of 96.7% for the diagnosis of untreated CD. These data indicate that measuring salivary anti-TG immunoglobulin-A is a valuable, noninvasive test that could be used for CD screening on a large scale in paucisymptomatic populations. Any suspicion of CD based on this test should be confirmed by the gold standard test, the demonstration of a typical villous atrophy of the duodenal mucosa.

Annick Ocmant, Ph
François Mascart, MD, PhD
Clinique d’Immunobiologie
Hôpital Erasme
Université Libre de Bruxelles
Brussels, Belgium
doi:10.1016/j.amjmed.2006.09.029

References
LETTER

The Reply:

The development of new, alternate, noninvasive methods of detecting celiac disease-associated antibodies is exciting, especially in view of the increasing realization that celiac disease is common, affecting approximately 1% of the population, and may be extremely diverse in its manifestations.1 The gold standard of diagnosis, however, remains the small intestinal biopsy taken at endoscopy.2 Previous studies have shown that both fecal and salivary antibody estimation are neither sensitive nor specific enough to be used for celiac disease diagnosis.3,4 The currently proposed test may be an improvement that requires greater validation. The recent development of rapid finger-stick blood tests that use tissue transglutaminase testing for in-office results may prove of value and be more accepted by medical practitioners.5

Peter H. R. Green, MD
Celiac Disease Center at Columbia University

References
Noninvasive Ventilation in Acute Heart Failure

To the Editor:

We read with interest the article “Diagnostic and Therapeutic Approach to Acute Decompensated Heart Failure,” wherein the authors discuss the management of acute decompensated heart failure. However, we were surprised to see no mention of the role of noninvasive ventilation (NIV) in acute heart failure (AHF). NIV is the application of mechanical ventilation without the use of an endotracheal airway and has been utilized for diverse forms of respiratory failure. The application of NIV to standard medical treatment of patients with acute respiratory failure not only prevents endotracheal intubation and its attendant complications, but also can decrease mortality in selected patients.

As early as 1936, continuous positive airway pressure (CPAP) has been shown to be an effective therapy for AHF. NIV augments the inspiratory flow, increases the tidal volume, and unloads the inspiratory muscles. It improves alveolar ventilation, re-expands flooded alveoli and prevents microatelectasis. By virtue of the above mechanisms, it decreases respiratory rate, and the work of breathing. The effective filling and emptying of the heart is determined in part by cardiac transmural pressure (P_{TM}), the pressure difference between the inside of the heart and the intrathoracic pressure. In patients with AHF, the amplitude of inspiratory swings is greater and results in higher P_{TM}. During systole, NIV increases the intrathoracic pressure and reduces venous return, thus decreasing the right and left ventricular preload; in diastole, NIV increases the pericardial pressure, reduces P_{TM}, and thus decreases afterload.

NIV also causes a decrease in the heart rate secondary to lung inflation and resultant increased parasympathetic tone. Recent evidence suggests that the use of CPAP in patients with AHF decreases intubation rate and improves survival.

However, therapy with NIV in AHF is probably beneficial only in patients with systolic dysfunction. In patients with predominantly diastolic dysfunction who require a relatively high filling pressure, the effects of positive pressure therapy can compromise venous return, resulting further in hypotension and prerenal azotemia.

Finally, which subgroup of patients should receive NIV? NIV is likely to benefit patients with severe AHF non-response to conventional medical therapy, presentation with a pH <7.25, or patients who are not candidates for intubation either because of a previous directive or as a result of poor prognosis due to underlying disease.

Ritesh Agarwal, MD, DM
Rajagopala Srinivas, MD
Department of Pulmonary Medicine
Postgraduate Institute of Medical Education and Research
Chandigarh, India
doi:10.1016/j.amjmed.2007.02.024

References
LETTER

The Reply:

We thank Agarwal and Srinivas for their comments on our article, “Diagnostic and Therapeutic Approach to Acute Decompensated Heart Failure,” published in The American Journal of Medicine.¹ The authors state that they were surprised to see no mention on the role of noninvasive ventilation in acute heart failure. Unfortunately, the authors missed our brief mention of this therapy in our manuscript. In the first paragraph of the “Therapeutic Interventions” section on page 123, we do, in fact, discuss this aspect of treatment as noted by the following sentences “Supplemental oxygen, noninvasive positive pressure ventilation, and mechanical ventilation are considered for hypoxemic and hypercarbic patients. Positive pressure ventilation decreases pulmonary edema, because increases in intrathoracic pressure decrease venous return.” Due to space limits, we could not provide a more detailed description of noninvasive positive pressure ventilation. We do appreciate, however, the in-depth discussion by the authors of this important therapy in patients with acute decompensated heart failure.

John R. Kapoor, MD, PhD
Section of Cardiology
Stanford University
Stanford, Calif

Mark A. Perazella, MD
Section of Nephrology
Yale University
New Haven, Conn

doi:10.1016/j.amjmed.2007.03.019

Reference

Endothelium-Independent Microvascular Dysfunction in Cardiac Syndrome X

To the Editor:

I read with interest the article by Hurst and colleagues. Although there is evidence that endothelial dysfunction is one of the pathologic mechanisms in the causation of cardiac syndrome X (CSX), endothelium-independent mechanisms also play a major role in the pathogenesis of cardiac syndrome. It seems that the reviewers have overlooked endothelial-independent microvascular dysfunction in their review.

Many studies have demonstrated the impaired endothelium-independent coronary microvascular dilatation in patients with CSX using different endothelium-independent coronary vasodilators (dipyridamole, papaverine, and adenosine). Opherk et al showed that coronary blood flow increased 3.8-fold in controls but only 2-fold in patients with CSX in response to administration of dipyridamole. Bottcher et al reported similar results. Chauhan et al reported a reduced augmentation of coronary blood flow in a CSX group (185% ± 74% vs 411% ± 59%, P < .0001) after administration of papaverine. Other investigators using cardiac magnetic resonance also demonstrated that adenosine administration did not increase myocardial perfusion index in the endocardium of patients with CSX, whereas it showed an increase in healthy controls.

These studies clearly indicate that in addition to endothelial dysfunction, endothelium-independent mechanisms such as impairment of smooth muscle relaxation also contribute to the pathogenesis of CSX.

Pankaj Madan, MD
Baylor College of Medicine
Houston, Tex

Ritu Madan, MBBS
Safdarjung Hospital
Delhi, India

doi:10.1016/j.amjmed.2006.07.041

References
LETTER

The Reply:

We appreciate the interest of Madan and Madan in our article on Cardiac Syndrome X (CSX).

We could not agree more that CSX is a complex disorder with a multifactorial mechanism. We also agree that there is evidence to support an endothelium independent component to this syndrome as they have cited and as manifest with a high frequency of chest pain during dipyridamole infusion in our clinical experience. While we did not want to deemphasize the importance of other mechanisms, the focus of our article was endothelium dependent microvascular dysfunction as a mechanism with clinical relevance in developing a treatment plan for these individuals. The hope is that future research will uncover effective therapy based on endothelium independent microvascular function.

Christopher P. Appleton, MD
R. Todd Hurst, MD
Mayo Clinic Graduate School of Medicine
Division of Cardiovascular Diseases
Mayo Clinic Arizona
Scottsdale

doi:10.1016/j.amjmed.2007.07.016
Communication Skills: A Call for Teaching to the Test

Anna Headly, MD, MFA
Director of Undergraduate Medical Education, Internal Medicine, UMDNJ/Robert Wood Johnson Medical School, Camden, NJ.

Educational authorities have been calling for improved physician-patient communication for decades, yet students and residents seem to feel less prepared than ever for difficult situations with patients, and patients are becoming less satisfied with physician communication skills.1,2 The Association of American Medical Colleges (AAMC) made communication central to its Medical Schools Outcomes Project,3 requiring medical students to pass a clinical skills examination as part of the United States Medical Licensing Examination (USMLE) Step 2. The clinical skills examination includes components of communication,4 but there is a paucity of data on the best methods to teach such skills.5,6 A recent large and costly intervention using a general communication skills curriculum resulted in only a 5% improvement in student scores.7 Most of the published approaches to the teaching of communication suffer from being vague, teacher-dependent, and non-reproducible. For instance, the Kalamazoo Consensus Statement on the essential elements of medical communication in medical encounters delineates 7 tasks, including “build the doctor-patient relationship” and “understand the patient’s perspective.”8 More recently, the Accreditation Council for Graduate Medical Education (ACGME) expanded its recommendations for communication competencies to include language such as “Be ‘present,’ paying attention to the patient” and “Demonstrate effective listening by hearing and understanding in a way that the patient feels heard and understood.”9 While these goals are admirable, they are not particularly useful when a student interacts with a patient. What students typically ask when given such vague guidelines is, “But what should I say?”

Effective physician-patient communication is central to patient care, and should therefore be a major emphasis of medical education. Yet teaching communication skills has historically been relegated to a sub-component of other curricula or limited to the basics of medical interviewing.10,11 The result is that most US medical graduates report little training (and less comfort) in end-of-life communication skills; most residents lack competence in delivering bad news and are unskilled in the use of interpreters; and physician-in-training scores of physician-patient communication in the primary care setting declined from 1996 to 1999.1,2,12,13 Not only is patient satisfaction affected by poor communication skills, but there is a significant correlation between effective physician-patient communication and improved health outcomes as well as reductions in malpractice claims.14,15

Educators have shied away from the idea of “teaching to the test” when it comes to communication skills, yet this reluctance leaves physicians-in-training ill-equipped when they are, in fact, tested.7,16 This is especially true for “higher order” communication skills; educators tend to approach emotionally charged discussions as very different from “routine” medical interviewing. For example, multiple sources give remarkably similar lists of specific questions to ask patients...
about chest pain (location, duration, timing, exacerbating and alleviating factors, quality, specific associated symptoms, etc), but very little advice is available on how to tell patients the diagnosis. When physicians-in-training enter into difficult discussions, they are forced to do so unrehearsed, which is a disservice to both the physician-in-training and the patient (and imparts the false message that “routine” interviewing is not emotionally difficult for physicians or patients).

Physician-in-training confidence in their general social communication skills might actually hamper performance in clinical interactions, which should not be surprising, as a person who is good at small talk in social settings may believe that connecting with patients is no different. Yet if physicians-in-training never practice saying “I’m afraid I have some bad news,” they are likely to find themselves at a loss when the time comes to relay bad news to a patient. Some small studies have shown that practicing communication skills tailored to specific situations can improve performance, and a randomized controlled trial in which residents were given step-by-step instruction and practice in interviewing for specific situations demonstrated improvement in residents’ abilities to conduct the medical interview. The General Internal Medicine Generalist Educational Leadership (GIMGEL) Group has published practical recommendations on clinical teaching of psychosocial aspects of patient care, which includes some specific questions addressing topics such as health literacy (“A lot of people have trouble reading things they get from the doctor because of all the medical words. Is it hard for you to read the things you get here?”). Specific statements made by clinicians enhance the satisfaction of critically ill patients’ families (eg, assurances that the patient will be comfortable and will not suffer). The next step is the development of a comprehensive curriculum based on clear statements such as these. Students need concrete, situation-specific tasks from which they can build communication skills.

The topic of physician-patient communication is broad, but it can be broken down into specific teachable components. For example, breaking bad news and conducting end-of-life discussions are important situations in which young physicians typically feel the most ill-prepared. Communicating with patients who have limited English proficiency is a rapidly growing problem. Discussing risks and benefits of procedures and obtaining informed consent has been emphasized by the US Agency on Healthcare Research and Quality as vital to patient autonomy and safety. These topics, while beyond the basics of the initial medical interview, still lend themselves to relatively simple scripts. The tasks should be specific and concrete, such as in the suggested sample scripts provided in the Table. Although exact statements made in each particular scenario will differ—obtaining informed consent for an HIV test is different than obtaining it for a high-risk surgical procedure—the specific tasks themselves (eg, explaining the diagnosis or the problem and explaining the proposed procedure) are fairly uniform. Educators will disagree about the most important scenarios to teach or the appropriateness of individual tasks, and the suggested scripts in the Table are intended to provoke discussion and new suggestions. Nevertheless, the underlying hypothesis—that communication skills should be taught by giving physicians-in-training explicit step-by-step skills rather than attempting to impart abstract concepts or attitudes—is not dependent on which particular tasks or situations are addressed. Some critics may argue that this approach risks creating automatons that mouth rigid scripts and ignore all the subtleties present in a patient interaction. On the contrary, giving students tools for and practice in making the kinds of statements that are known to be effective in specific situations will help students unlock the mysteries of difficult patient interactions and go on to build unique physician-patient relationships.

<table>
<thead>
<tr>
<th>PERSPECTIVES VIEWPOINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Effective physician-patient communication is central to patient care.</td>
</tr>
<tr>
<td>● Communication skills should be a major emphasis of medical education.</td>
</tr>
<tr>
<td>● Communication “scripts” are a useful tool in medical education curricula.</td>
</tr>
</tbody>
</table>
care, but they also should insist on evidence-based education. A great deal of curriculum development is occurring in the country, but it is rarely subjected to controlled evaluation, meaning that there is almost no evidence upon which to select elements of a curriculum. Adding elements to a curriculum comes at an expense in terms of both time and money, so educators need to know what works and what does not. However, for rigorous evaluation of communication teaching methods to be possible, a generally agreed-upon set of critical elements of communication in different settings needs to exist.

Once a communications curriculum is constructed, methods are already in place for teaching and evaluating it. Role-playing is an effective technique for teaching communication skills to medical students as are standardized patient workshops. Watching clinicians at work is an invaluable learning experience and while it is unfortunately not feasible for every physician-in-training to be apprenticed to an expert communicator, the use of digital teaching formats shows promise. Objective structured clinical examinations (OSCEs) are a widely accepted examination technique for clinical competence, including competence in communication. Moreover, OSCEs are similar in format to the clinical skills examination portion of USMLE Step 2.

New guidelines are mandating that medical education incorporate ideals of patient-centered care, ethics, professionalism, and humanism, and communication skills are central to all of these ideas. To date, no method for achieving these goals has been described. Although it is admittedly hard to teach appropriate behavior and harder still to measure it, reaching a consensus on the framework of appropriate communication would provide medical educators with a common starting point and provide students with the skills to hit the right notes with patients.

ACKNOWLEDGMENT

The author thanks Michael Picchioni, MD, and Joshua P. Metlay, MD, for their helpful comments on earlier drafts of this essay.

References


41. Vu NV, Barrows HS. Use of standardized patients in clinical assessments: Recent developments and measurement findings. Educational Researcher. 1994;23(3).


The Heroic Physician and *The Gross Clinic*

Helle Mathiasen, Cand Mag., PhD
Program in Medical Humanities, University of Arizona College of Medicine, Tucson.

I never knew of but one artist, and this is Tom Eakins, who could resist the temptation to see what they think ought to be rather than what is.

—Walt Whitman

“One painting, many visitors – ‘The Gross Clinic’ is a hit in its new home. Eakins’s masterpiece went on display at the Art Museum. It was worth the fuss, they said.”

—Philadelphia Inquirer, January 6, 2007

This headline announces the arrival and display of an important medical painting at the Philadelphia Museum of Art.

In 1875, Dr. Gross’s students commissioned Philadelphia-born painter Thomas Eakins (1844-1916) to create a portrait of the distinguished surgeon Dr. Samuel Gross (1805-1884). Eakins chose to show his teacher at work in the operating theater at Jefferson Medical College. The venerable Dr. Gross was about to retire, and his students wanted to honor him. They bought the work from Eakins for $200 and donated it to Jefferson Medical College. One hundred thirty-two years later, in January 2007, as Jefferson Medical College was getting ready to put it up for sale, Christie’s valued the painting at $68 million. After an intensive local and national fundraising campaign, the Pennsylvania Academy of the Fine Arts and the Philadelphia Museum of Art purchased Eakins’s most controversial painting in joint ownership. Although too avant-garde for 19th-century Philadelphia, Eakins’s representation of the blood and nudity of surgical practice in *The Gross Clinic* has been praised as “...the greatest single painting in the history of American art” (p 190).

At 30 years of age, Eakins wrote to a friend, “I have just got a new picture blocked in and it is far better than anything I have ever done” (p 181). Eakins decided to submit his portrait of Dr. Gross as an entry for the Philadelphia Centennial Exhibition of 1876. However, the Centennial Selection Committee judged the work unfit for display in the Main Exhibition Hall. It was hung in a side gallery among army medical exhibits. Critics condemned the painting for its representation of a surgeon’s bloody hand and scalpel, claiming it was unsuitable for ladies and children to look at. The patient’s nude, lower body prominently displayed was another source of outrage. This censure caused the artist great disappointment.

In the painting (Figure), we see Dr. Gross in the amphitheater at Jefferson Medical College performing an operation for which he was famous: removing infected bone from a young patient with osteomyelitis of the femur. Earlier
treatments of osteomyelitis often had resulted in amputation, but Dr. Gross had perfected a surgical procedure involving anesthesia. The painting’s composition is a triangle, its apex Dr. Gross’s head. The surgeon holds a bloody scalpel between his right thumb and forefinger; he turns to the right, away from the patient, lecturing to students and faculty in the audience. On his left is the bed with the young patient reclining on his right side, his buttocks and sock-clad feet toward the viewer. In the foreground, we see a table covered with surgical instruments. The sole woman in the painting is dressed in black and sits below Dr. Gross’s right hand. Possibly the patient’s mother, she lifts her arms and curls her fingers in front of her face in a protective gesture.

The 5 men assisting the surgeon have been identified by name. The anesthesiologist presses a chloroform-soaked cloth onto the patient’s face; another physician is scraping the patient’s femur; a third pulls the retractor holding the wound open, and a fourth holds the patient’s feet. The fifth assistant is invisible. We glimpse his thumb pulling the other retractor beneath Dr. Gross’s left elbow. The person writing in the front row is the Medical College recorder. Eakins has painted himself drawing or writing to the viewer’s right. In the background, the artist has placed dark figures of spectators, some of whom have been identified.

The artist emphasizes the drama of the operating theater by his use of chiaroscuro, a technique made famous by Rembrandt in his painting “The Anatomy Lesson of Dr. Tulp.” Most of the picture is dark, but significant light falls on Dr. Gross’s head and hand, the sheet, and the patient’s lower body. Eakins illuminates the surgeon’s high forehead, creating an aura of his gray hair. The light symbolizes the doctor’s remarkable intellect. The heroic physician stands erect, master of himself and his task. The cringing woman on his right may embody the uneducated layperson who reacts emotionally to seeing a child’s blood and exposed, nude body.

Eakins’s wife, the painter Susan Macdowell Eakins, said that her husband contemplated becoming a physician or an artist. He began studying anatomy, physiology, and dissection with physicians already as a student at Central High School in Philadelphia. He enrolled as a medical student at Jefferson Medical College in 1864, and continued his study of the human body at the Pennsylvania Academy of Fine Arts (p 20). He attended anatomical classes, drawing classes, and Dr. Gross’s surgical clinics. While an art student in Paris from 1866 to 1869, Eakins dissected and witnessed surgical clinics at Paris Hospitals and the École de Medicine. During this period, he took drawing and painting classes where live nude models were used. Returning to Philadelphia, he continued anatomy and dissection classes, later telling an interviewer: “No one dissects to quicken his eye for, or his delight in, beauty. He dissects simply to increase his knowledge of how beautiful objects are put together to the end that he may be able to imitate them” (p 55). Eakins’s fascination with the body profited his art, as evidenced in The Gross Clinic, but it hindered his career advancement.

Eakins became a popular teacher at the Pennsylvania Academy of the Fine Arts, where he launched a number of curricular modifications, including teaching his students to work from live nude models. Because of the difficulty of finding models, especially women, he asked some of his students to pose nude and did so himself. In addition, he painted and photographed some of his students in the nude in the studio and outdoors. The Pennsylvania Academy Board regulations prohibited students from studying nude models in mixed classes. As a consequence of his rebellion against these rules, Eakins was forced to resign his faculty position.

Although his personal life continued to be unconventional, none of the artist’s work after The Gross Clinic caused similar controversy. Eakins became an esteemed painter of athletes; he painted portraits of people he admired, including 25 Philadelphia physicians. His contemporary and fellow American master Walt Whitman recognized Thomas Eakins’s true genius, as art historians do today (p 144).

References