Left Atrium Size and the Risk of Cardiovascular Death in Middle-aged Men

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Background: The echocardiographic identification of subclinical risk markers may enhance risk stratification for the development of cardiovascular outcomes in the general population. Although echocardiography is widely used in the evaluation of cardiac structures and function, the prognostic value of echocardiographic assessment of left atrium (LA) size for risk stratification of cardiovascular death is unknown.

Methods: Left ventricular (LV) mass and LA size were measured by using M-mode echocardiography in a representative population-based sample of 830 men (age, 42-61 years) from eastern Finland. There were 54 deaths due to cardiovascular disease during an average follow-up of 13 years.

Results: The strongest risk factors for cardiovascular death were smoking, family history of coronary heart disease, low exercise capacity, elevated blood pressure, exercise-induced myocardial ischemia, and large LA diameter. Men in the highest tertile of LA diameter (>43 mm) had a 2.3-fold (95% confidence interval, 1.1-5.0) risk of cardiovascular death compared with men in the lowest tertile of LA diameter (<39 mm), after adjusting for other risk factors and the use of antihypertensive medications. The excess risk for cardiovascular mortality appeared to reside largely in the highest tertile of LA size. After additional adjustment for LV mass, the relation between LA size and mortality did not remain statistically significant (relative risk, 1.5; 95% confidence interval, 0.8-4.1; P=.15) in this group.

Conclusions: This prospective population-based study shows that echocardiographically defined LA diameter was directly related to the risk of cardiovascular death. The association of LA enlargement to cardiovascular death appears to be partially related to LV hypertrophy.

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Many previous studies evaluating cardiovascular risk place an emphasis on the presence of clinical disease such as hypertension, diabetes mellitus, and hyperlipidemia but minimize mechanistic markers that may be predictive for various outcomes. The efforts stem from an appreciation that atherosclerosis and subclinical diseases begin at a young age, but cardiovascular diseases (CVDs) are clinically silent for many years. During these years of latent period of disease, it is possible to delay or prevent the onset of systemic clinical manifestations. The noninvasive echocardiographic identification of subclinical risk markers may enhance risk stratification for the development of cardiovascular events in a population who may be at an increased risk.

The associations between left ventricular (LV) hypertrophy and coronary heart disease (CHD) death have been described. Increased LV mass as detected by echocardiography is a strong independent predictor of cardiovascular morbidity, especially in hypertensive men. In previous studies, age and body weight and cardiovascular features such as the duration of atrial fibrillation, LV mass, annular calcification, the severity of coronary artery disease, and hypertension have been related to left atrium (LA) size.

Transesophageal echocardiography may significantly increase our ability to assess the risk for CVDs. Left atrium size can be readily obtained with any echocardiographic system. However, the prognostic value of LA size to the risk of death due to CVD in the general population remains largely unexplored. Thus, we investigated the prognostic significance of the LA diameter with regard to the risk of death due to CVD in a population-based sample of men.
METHODS

PARTICIPANTS

The analyses were carried out with the participants of the Kuopio Ischaemic Heart Disease (KIHD) Risk Factor Study, a longitudinal population-based study designed to investigate risk factors for CVD, atherosclerosis, and related outcomes. The study population is a representative sample of men living in the city of Kuopio, Finland, and its surrounding rural communities, who were aged 42 to 61 years at baseline. The examinations were performed between March 1984 and December 1989. Of 3235 potentially eligible men, 2682 (83%) volunteered to participate. The KIHD Risk Factor Study was approved by the Research Ethics Committee of the University of Kuopio, and each participant gave written informed consent.

The study reported herein is based on data obtained from 981 participants who had available data on echocardiographic measurements at baseline. All men who visited the clinics between 1986 and 1988 participated in the echocardiographic measurements. Men were excluded if they had a history of myocardial infarction, stroke, or cardiac insufficiency; unreadable data on any LV mass measures; or systemic hypertension; presence of diabetes mellitus, or any ST depression of 1.0 mm or more at 80 milliseconds after J point or any ST depression of 1.0 mm or more at 80 milliseconds after J point. Exercise capacity was measured by maximal oxygen uptake, which was defined as the highest value for or the plateau in oxygen uptake.

CARDIAC ULTRASONOGRAPHY

Echocardiographic studies were performed with an ATL Ultramark IV system (Advanced Technology Laboratories, Bothell, Wash) using 2-dimensional-guided M-mode measurements with a 3.0- or 3.5-MHz transducer. Two-dimensional–guided M-mode images were obtained from the parasternal window and a perpendicular projection across the heart, with participants lying in a modified left lateral decubitus position. Left atrium diameter, aortic root diameter, LV end-diastolic internal dimension, end-diastolic thickness of the interventricular septum, end-diastolic thickness of the LV posterior wall, and LV systolic function (fractional shortening percentage) were among the measures collected. All measures were calculated from leading edge to leading edge. Left atrium diameter was measured in the parasternal long axis view from trailing edge of the posterior aortic root-anterior LA complex to the posterior LA wall at end-systole. Left ventricular mass was calculated by using the Devereux formula (corrected American Society of Echocardiography cube method). The reproducibility of this measure was tested in a random sample of 30 subjects reexamined at a 3-week interval, yielding a retest reliability of 0.82. Left atrium size was analyzed as a linear dimension, as well as indexed by height, body mass index (BMI), and body surface area. Left ventricular mass measures are typically adjusted for body surface area. We used a body surface area–adjusted approach in this study similar to a previous cross-sectional KIHD Risk Factor Study. All the echocardiographic measurements were performed and interpreted by 1 cardiologist (J.E.) according to standardized protocol.

BLOOD PRESSURE DETERMINATION

Resting blood pressure was measured by an experienced nurse using a random-zero sphygmomanometer (cuff size, 14 × 54 cm; Hawksley & Sons Limited, Lancing, England) after 5 and 10 minutes of rest in a seated position in a quiet room between 8 AM and 10 AM.

EXERCISE TEST

A maximal symptom-limited exercise tolerance test was performed using an electrically braked cycle ergometer. The electrocardiogram was registered continuously during the test. The electrocardiographic criteria for ischemia during exercise were horizontal or downsloping ST depression of 1.0 mm or more at 80 milliseconds after J point or any ST depression of 1.0 mm or more at 80 milliseconds after J point. Exercise capacity was measured by maximal oxygen uptake, which was defined as the highest value for or the plateau in oxygen uptake.

ASSESSMENT OF OTHER COVARIATES

The collection of blood specimens and measurement of fasting levels of serum lipids and assessment of smoking and presence of diabetes mellitus are described elsewhere. The life-long exposure to smoking (cigarette pack-years) was estimated as the product of the number of smoking years and the number of tobacco products smoked daily at the time of examination. Body mass index was computed as weight in kilograms divided by the square of height in meters. Family history of CHD was defined as premature CHD in parents or in first-degree relatives before the age of 55 years in men.

ASCERTAINMENT OF FOLLOW-UP EVENTS

Every resident of Finland has a unique personal identifier (PID) that is used in registers. Follow-up for cardiovascular outcomes was done using the PIDs. Deaths were ascertained by linkage to the national Causes of Death Register using the PIDs. There were no losses to follow-up. All deaths that occurred between study entry (March 1986–December 1989) and December 2001 were included. Cardiovascular causes of deaths were coded according to the International Classification of Diseases, Ninth Revision codes 400-459 and International Statistical Classification of Diseases, Tenth Revision codes 100-199.

STATISTICAL ANALYSIS

Descriptive data are presented as mean ± SD for continuous data and percentages for categorical data. The associations of echocardiographic data with the risk of CVD death were analyzed using risk factor–adjusted Cox proportional hazards models. The cumulative risk of mortality from CVDs by the LA size was calculated using the Kaplan-Meier method. The correlations between LA size, LV mass, and risk factors were analyzed using the Pearson correlation test, and the most important predictors for LA size were analyzed using linear regression model. To demonstrate the predictive value of echocardiographic data, LA diameter was entered into a forced Cox model including previously documented risk factors (age, examination year [1986-1988], cigarette smoking, diabetes mellitus, systolic blood pressure, family history of CHD, physical fitness, exercise-induced myocardial ischemia, BMI, serum low-density lipoprotein, and high-density lipoprotein cholesterol) and the use of antihypertensive medications. Additional adjustment was made by using echocardiographically determined LV hypertrophy and LV systolic function.

The analysis of tertiles divided the subjects into thirds based on the distribution of LA size observed in the sample. The tertiles were slightly uneven because LA dimension was measured to the nearest millimeter. Relative risks (RRs), adjusted for risk factors, were estimated as antilogarithms of coefficients for independent variables. Their confidence intervals (CIs) were estimated under the assumption of asymptotic normality of the estimates. P <.05 was considered statistically signifi-
RESULTS

BASELINE CHARACTERISTICS

Baseline characteristics are given in Table 1. Mean LA diameter was 41.4 ± 5.4 mm (range, 21-62 mm) and mean LV mass was 207.1 ± 53.9 g (range, 91.6-525.1 g). Prevalence of LV hypertrophy, as defined by LV mass greater than 125 g/m², was 18% (n=147). Echocardiographic characteristics are shown according to fatal cardiovascular events in Table 2. Mean LA diameter was higher among men with subsequent cardiovascular death (43.7 mm vs 41.2 mm). The prevalence of atrial fibrillation was 2%, and the incidence of atrial fibrillation was 0.5% per year.

The crude correlation between LA diameter and LV mass was r=0.47 (P<.001). Body weight was another variable that was clearly correlated with LA diameter (r=0.47; P<.001). In a multivariable regression model, age (P<.001), BMI (P<.001), the use of antihypertensive medications (P=.001), low exercise capacity (P<.001), and elevated systolic blood pressure (P=.03) were predictors of increased LA diameter (per 5 mm).

ASSOCIATED RISK FACTORS

During a 13-year follow-up period, there were 135 all-cause deaths, 69 of which were due to cardiovascular causes. The strongest risk factors for all-cause death were smoking (P<.001), systolic blood pressure (P=.001), exercise capacity (P=.003), and LA diameter divided by BMI (P=.04), after adjusting for all the variables given in Table 3 (model 2). The risk factors for CVD death were smoking (P<.001), exercise capacity (P=.002), family history of CHD (P=.002), systolic blood pressure (P=.01) exercise-induced myocardial ischemia (P=.02), and LA diameter divided by BMI (P=.047). Similarly, after additional adjustment for LV systolic function, the results were identical to those in model 3 (Table 3).

LA SIZE, LV HYPERTROPHY, AND CARDIOVASCULAR RISK

The adjusted risk for cardiovascular death were 1.23-fold (95% CI, 0.98-1.60; P=.07) for each 5-mm increase.
The relation between LA size and mortality did not reproducible in previous studies.9,10 It has been hypoth-
thesized that LA size represents the integration of LV di-
astolic performance over time. Hence, LA volume provides a noninvasive clinical measure for identifying men with heightened risk of death.

Large LA diameter as indexed by height and body surface area was a strong predictor for an increased risk of cardiovascular death. When LA diameter (in millimeters) was divided by height (in meters), a 1-U increment in this variable was related to a 1.11-fold (95% CI, 1.02-1.21; P = .02) risk for cardiovascular death, after adjustment for other risk factors and the use of antihypertensive medications. The RR was 1.15 (95% CI, 1.02-1.31; P = .02) when LA was indexed for body surface area (meters squared). Those men with a height-indexed LA dimension greater than 25.2 mm/m had a 2.48-fold (95% CI, 1.49-5.88; P = .03) risk of cardiovascular death compared with those with an LA dimension less than 22.5 mm/m, after adjustment for risk factors.

**COMMENT**

This prospective study shows that echocardiographically defined LA diameter was related to an increased risk of CVD death in a representative eastern Finnish male population. Based on our findings, LA size adds to the prognostic value of M-mode echocardiography and provides a noninvasive clinical measure for identifying men with heightened risk of death.

We found that smoking, family history of CHD, low exercise capacity, elevated blood pressure, and exercise-induced myocardial ischemia were independent predictors for death due to cardiovascular causes, even when echocardiographic measurements were taken into account. Our study showed, however, that LV hypertrophy can be considered one of the most important echocardiographic risk predictors in addition to LA size. When LV hypertrophy was included in the multivariate model, the predictive value of LA size weakened considerably. This implies that these 2 measures are interrelated, and the correlation between LA size and LV mass was comparable with previous studies.9,10 It has been hypothesized that LA size represents the integration of LV diastolic dysfunction, regardless
of whatever loading conditions and filling pressure are present at the time of examination. It was found that LV hypertrophy, defined as a higher LV mass, is detected by echocardiography in 16% to 19% of a general population and at least in 23% of hypertensive subjects. In our study, with a representative sample of middle-aged men, the prevalence of LV hypertrophy (defined by an LV mass of greater than 125 g/m²) was 18%, which is in accordance with previous studies. In the apparently healthy and hypertensive populations, atrial enlargement has also been common, reflecting the burden of LV hypertrophy.

The important message is that large LA diameter may be due to a sustained elevation in LV filling pressure in the absence of other contributing pathologic conditions such as congestive heart failure and mitral valve disease. In this study, CVDs were uncommon and thus alone cannot explain the observed results regarding the increased risk of cardiovascular death related to LA size. However, age, BMI, the use of antihypertensive medications, low exercise capacity, and elevated systolic blood pressure were predictors of increased LA diameter.

It is proposed that M-mode echocardiographic LA enlargement is a useful marker of advanced hemodynamic changes, which are related to the severity of angiographically documented coronary artery disease. The increase in myocardial mass lowers coronary reserve, enhances cardiac oxygen requirements and impairs LV filling and contractility. Hypertension, obesity, advanced age, and valvular heart disease can lead to both LV hypertrophy and LA enlargement. On the other hand, LV hypertrophy as well as LA size can be reduced by specific antihypertensive therapy. The left ventricle adapts to an increased afterload such as that produced by arterial hypertension with concentric LV hypertrophy. Consistent with our findings, the relation of LA enlargement to death may be partially mediated by increased LV mass.

Previous studies have identified a number of echocardiographic variables that predict CVDs and prognosis, but those studies were not focused on population-based studies. Many of those studies showed the value of LA size as a risk marker were based on clinical populations including subjects who were referred because of various symptoms such as dyspnea, chest discomfort, palpitations, murmurs, chest discomfort, syncope, or presyncope. There are few studies that have considered echocardiographic findings as predictive variables of risk in asymptomatic individuals. One exception is the Framingham Heart Study, which has shown the predictive value of LV hypertrophy. In another study, the authors did not show the value of LA size as a risk predictor for cardiac events, although it was predictive for stroke. In a large prospective population-based study including elderly subjects, selected 2-dimensional M-mode echocardiographic measurements were important markers of subclinical disease and conferred independent prognostic information for incident cardiovascular events. The recent findings from older residents in Olmsted County, Minnesota, showed that echocardiography in general and LA volume can be included as variables offering insight into the cardiovascular risk.

The strengths of this study include its prospective population-based design with reliable data on various causes of diseases as specific major outcomes that were prospectively ascertained through the Finnish National Discharge and Death Registry using PID codes, supplemented with data on echocardiography, health status, and risk factors. Our study emphasizes the importance of the measurement of LA size by echocardiography in a middle-aged male population from eastern Finland, but whether the same association between the LA size and mortality from cardiovascular causes exists in women and other races requires further studies. Compared with other echocardiographic studies in the United States, our study shows the importance of LA size in a relatively young population in Europe. We used LA size indexed to height because it is considered to be an intrinsic variable of body size that attempts to avoid problems associated with overcorrection for the effect of obesity on body size.

The availability of the latest echocardiographic technology was limited at the time of baseline examinations. In this study, we did not measure mitral or pulmonary flow velocities and tissue Doppler velocities, which can be used as diagnostic tools in clinical practice today. A limitation of M-mode echocardiography is its insensitivity for detection of valvular heart disease. However, our main objective was to provide an additional simple prognostic marker that may enhance the usefulness of echocardiography for risk stratification in a population, although this study does not show if subjects with LA enlargement should be treated more aggressively, as patients with hypertension, LV hypertrophy, or diabetes are normally treated. Our prospective study suggests that the easily obtainable LA diameter measurement can be used as a prognostic marker when instruments to measure mitral or pulmonary vein velocity or any other new technologies are not available.
This study provides evidence that LA size is a noninvasive parameter that improves risk stratification for fatal cardiovascular events in a population-based cohort, and the relation of LA enlargement to death appears to be partially mediated by LV mass. Left atrium size is a nontraditional clinical risk stratifier, but it may be a more important measure in preclinical CVDs.

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