Left Ventricular End-Diastolic Pressure Predicts Survival in Coronary Artery Bypass Graft Surgery Patients

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Background. There is a known association between a depressed left ventricular ejection fraction (LVEF < 0.35) and increased mortality in patients undergoing coronary artery bypass graft (CABG) operations. Recent studies show that elevated preoperative LV end-diastolic pressure (LVEDP) is an independent predictor of operative death for patients undergoing CABG. Therefore, the purpose of this study was to define the long-term predictive value of elevated LVEDP in CABG and its relationship to LVEF.

Methods. Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH), a clinical data collection initiative capturing all patients undergoing isolated CABG in Alberta, Canada, was used to identify 6,735 consecutive patients who had LVEDP and LVEF data recorded by catheterization undergoing isolated CABG between 1996 and 2011. Patients were divided into four groups based on LVEF and LVEDP: group 1 (LVEF ≥ 0.35, LVEDP < 18 mm Hg), group 2 (LVEF < 0.35, LVEDP < 18 mm Hg), group 3 (LVEF ≥ 0.35, LVEDP ≥ 18 mm Hg), and group 4 (LVEF < 0.35, LVEDP ≥ 18 mm Hg).

Results. Patients with an LVEF > 0.35 had improved long-term survival compared with patients with depressed LVEF (LVEF < 0.35, p < 0.001). In patients with a depressed LVEF, an elevated LVEDP was associated with decreased long-term survival (group 2 vs 4, p < 0.001). Other significant independent predictors for death were age, chronic obstructive pulmonary disease, peripheral vascular disease, dialysis dependence, and congestive heart failure (p < 0.001). Isolated elevated LVEDP was not an independent risk factor for long-term mortality.

Conclusions. In patients with a depressed LVEF, an elevated LVEDP is associated with poor long-term survival. These data support the added value of long-term prognostic value of LVEDP in patients with depressed LVEF undergoing CABG.

(Risk stratification is an important preoperative assessment in patients undergoing coronary artery bypass graft (CABG) operations [1–6]. Risk factors for CABG have been well established and validated by several investigators, leading to the adoption of scoring risk models such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE) [7] and the bedside Bernstein-Parsonnet score [5, 8]. Outcomes of patients undergoing isolated CABG with depressed left ventricular ejection fraction (LVEF) have improved as a result of advances in surgical techniques, myocardial protection, and improved long-term medical management after CABG. However, a depressed LVEF continues to be strongly associated with increased mortality in patients undergoing isolated CABG surgery [9, 10].

The importance of preoperative LV end-diastolic pressure (LVEDP) as an independent predictor of death in isolated CABG is uncertain. Elevated LVEDP has been associated with declining survival in cardiac surgery, although in most studies, elevated LVEDP is not an independent risk factor for death [1, 3, 4, 7]. Elevated LVEDP may represent multifactorial cardiac dysfunction, including systolic, diastolic, or mixed LV dysfunction [11].

Because quantitative echocardiographic evaluation of diastolic dysfunction is often not performed on all patients undergoing CABG, we accept elevated LVEDP as a surrogate for cardiac compromise with mixed etiologies. LVEDP is accessible for most patients undergoing elective or urgent CABG where a left ventricular angiogram is performed routinely to quantify LVEDP. In the present study, we aimed to examine the long-term predictive value of elevated LVEDP in patients undergoing isolated CABG and the relationship between LVEDP and LVEF.

Accepted for publication Oct 22, 2013.
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Published by Elsevier Inc

http://dx.doi.org/10.1016/j.athoracsur.2013.10.047

0003-4975/53.00

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Patients and Methods

This study was approved by the University of Alberta Health Research Ethics Board–Biomedical Panel as acceptable within the limitations of patient outcomes research. Individual patient consent was waived because no individual patients were identified in the study.

Data Source

Data were collected from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database. This database is a prospective data collection initiative that gathers real-time data from all patients in all hospitals that provide cardiac catheterization and coronary revascularization in Alberta, Canada, beginning at the patient's referral for cardiac catheterization. Data are entered into the APPROACH registry along the patient's clinical trajectory. APPROACH contains demographic data and patient risk factors, comorbidities, other diagnoses, and procedural data. Adverse events data are also recorded in the APPROACH database and reviewed through various hospital-based morbidity and mortality rounds. Because the data in the APPROACH registry are used for clinical and administrative purposes, software checks have been put into place to ensure that there are limited missing data, particularly in the baseline characteristics of the patients in APPROACH [12]. Furthermore, for the purposes of research, we annually use a data replacement method that has been validated and ensures that the data are more than 95% complete [12].

From this base, patients are monitored longitudinally for the determination of short-term and long-term outcomes [13]. Vital statistics from the Alberta Bureau of Vital Statistics are merged quarterly with the APPROACH registry and were merged December 31, 2011, for this cohort. The purpose of this quarterly merge is to update the APPROACH registry and validate deaths that were entered independently (in-hospital or family identified) during the previous 4 months.

Study Cohort

In this study, cardiac catheterization or echocardiography, or both, were used to measure LVEF and LVEDP. Included were 6,735 consecutive patients who had isolated CABG in Alberta between January 1, 1996, and December 31, 2011. Patients undergoing concomitant cardiac surgical procedures and transplant recipients were excluded from this cohort. Patients were divided into four groups according to LVEF and LVEDP: group 1—LVEF 0.35 or more, LVEDP of less than 18 mm Hg; group 2—LVEF of less than 0.35, LVEDP of less than 18 mm Hg; group 3—LVEF of 0.35 or more, LVEDP of 18 mm Hg or more; group 4—LVEF of less than 0.35, LVEDP of 18 mm Hg or more.

Statistical Analysis

Preoperative categoric variables were compared among the four groups by \( \chi^2 \) test for independence (degrees of freedom = 3), and continuous variables (age and body mass index) were compared by one-way analysis of variance with post hoc Bonferroni correction. Long-term survival after CABG was estimated using Kaplan-Meier actuarial log-rank statistics for the four groups. Multivariate regression using Cox proportional hazards modeling was used to determine independent risk factors for death for all patients analyzed in the cohort.

Results

Preoperative Characteristics

Isolated CABG was performed in 6,735 patients (18.2% female) with a mean age of 66 ± 11 years. The baseline characteristics and significance are summarized in Table 1. The four groups were similar in age; there were significantly fewer women with depressed LVEF (groups 2 and 4). Preoperative risk factors were similar among the four groups for history of cerebrovascular disease, dialysis-dependent renal failure, peripheral vascular disease, hypertension, dyslipidemia, malignancy, liver disease, prior percutaneous coronary intervention, and prior CABG. Patients with a depressed LVEF (groups 2 and 4) had a higher incidence of chronic obstructive pulmonary disease, congestive heart failure, history of smoking, and history of myocardial infarction (\( p < 0.01 \)).

Coronary Angiography

The indications for angiography and anatomy of coronary disease are summarized in Table 2. Group 4 was significantly more likely to require angiography for the indication of ST-elevation myocardial infarction. As well, groups 2 and 4 were significantly more likely to have 2 or 3 significantly diseased coronary arteries than groups 1 and 3. However, the incidence of left main disease was similar among the four groups.
Table 1. Baseline Characteristics

| Variable | Group 1 (EF ≥0.35, LVEDP <18 mm Hg) (n = 2,627) | Group 2 (EF <0.35, LVEDP <18 mm Hg) (n = 105) | Group 3 (EF ≥0.35, LVEDP ≥18 mm Hg) (n = 3,506) | Group 4 (EF <0.35, LVEDP ≥18 mm Hg) (n = 497) | p Value
---|---|---|---|---|---
Female, % | 16.8 | 16 | 20.1 | 12.8 | <0.001
Age, years | 65.8 ± 10.2 | 67.3 ± 9.0 | 66.5 ± 10.2 | 65.4 ± 10.0 | 0.005
BMI, kg/m² | 28.9 ± 5.4 | 28.4 ± 5.6 | 30 ± 6.0 | 29.5 ± 6.0 | <0.001
CVD, % | 8 | 8.4 | 8.1 | 9.4 | 0.45
COPD, % | 14.8 | 22.4 | 16.7 | 27.2 | <0.001
CHF, % | 5 | 29 | 7.9 | 33.3 | <0.001
DM Type, % | 1 | 2 | 1.5 | 2.1 | 0.27
Age, years | 65.8 ± 10.2 | 67.3 ± 9.0 | 66.5 ± 10.2 | 65.4 ± 10.0 | 0.005
BMI, kg/m² | 28.9 ± 5.4 | 28.4 ± 5.6 | 30 ± 6.0 | 29.5 ± 6.0 | <0.001
CVD, % | 8 | 8.4 | 8.1 | 9.4 | 0.45
COPD, % | 14.8 | 22.4 | 16.7 | 27.2 | <0.001
CHF, % | 5 | 29 | 7.9 | 33.3 | <0.001
DM Type 1, % | 1 | 2 | 1.5 | 2.1 | 0.27
Age, years | 65.8 ± 10.2 | 67.3 ± 9.0 | 66.5 ± 10.2 | 65.4 ± 10.0 | 0.005
BMI, kg/m² | 28.9 ± 5.4 | 28.4 ± 5.6 | 30 ± 6.0 | 29.5 ± 6.0 | <0.001
CVD, % | 8 | 8.4 | 8.1 | 9.4 | 0.45
COPD, % | 14.8 | 22.4 | 16.7 | 27.2 | <0.001
CHF, % | 5 | 29 | 7.9 | 33.3 | <0.001
DM Type 2, % | 28.2 | 28 | 32.4 | 40 | <0.001
Dialysis, % | 0.5 | 1 | 1.2 | 1.6 | 0.07
Hypertension, % | 71.9 | 76.5 | 76.4 | 70.6 | 0.002
Dyslipidemia, % | 83.6 | 90.3 | 84.5 | 78.5 | 0.02
PVD, % | 7.4 | 11.6 | 6.8 | 8.5 | 0.11
Smoking, % | 21.8 | 32.1 | 22.4 | 35.5 | <0.001
Malignancy, % | 4.5 | 4.2 | 4.8 | 4 | 0.44
Liver disease, % | 0.9 | 0 | 0.7 | 0.2 | 0.15
GI disease, % | 9.3 | 6.2 | 9.1 | 7 | 0.01
Prior MI, % | 23.7 | 46 | 25.8 | 37.7 | <0.001
Prior PCI, % | 16.3 | 20.2 | 17.7 | 14.3 | 0.07
Prior CABG, % | 1.4 | 2 | 2.1 | 3.5 | 0.05

BMI = body mass index; CABG = coronary artery bypass grafting; CVD = cerebrovascular disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; EF = ejection fraction; GI = gastrointestinal; GI = gastro-intestinal; LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease.

Postoperative Survival Analysis

The mean length of follow-up was 4.55 ± 2.49 years, with all patients tracked by vital statistics for complete survival data. The 30-day mortality rates for groups 1, 2, 3, and 4 were 1.5%, 4.8%, 2.5%, and 7.2%, respectively (p < 0.001). Patients with a depressed LVEF (groups 2 and 4) had increased 30-day mortality of 6.78% compared with 2.07% in patients with an LVEF exceeding 0.35 (groups 1 and 3; p < 0.001). The 8-year survival for groups 1, 2, 3, and 4 was 88.6%, 81%, 87.2%, and 70.2%, respectively (p < 0.001). The Kaplan-Meier estimates of survival identified that the groups 1 and 3, with an LVEF exceeding 0.35, had improved long-term survival compared with groups 2 and 4 with depressed LVEF (87.9% vs 72.1%, p < 0.001; Fig 1).

Table 2. Preoperative Coronary Angiography

| Variable | Group 1 (EF ≥0.35, LVEDP <18 mm Hg) (n = 2,627) | Group 2 (EF <0.35, LVEDP <18 mm Hg) (n = 105) | Group 3 (EF ≥0.35, LVEDP ≥18 mm Hg) (n = 3,506) | Group 4 (EF <0.35, LVEDP ≥18 mm Hg) (n = 497) | p Value
---|---|---|---|---|---
Indication for angiography
Stable angina, % | 10.3 | 9.6 | 12.5 | 6.8 | 0.01
Unstable angina, % | 19.7 | 14.4 | 13.8 | 12 | 0.05
STEMI % | 8 | 8.7 | 11.6 | 19.3 | <0.001
NSTEMI % | 21.5 | 26 | 21.7 | 29.1 | 0.07
Other, % | 40.5 | 41.3 | 40.4 | 32.7 | 0.05
Coronary anatomy
<50% | 0.8 | 0 | 0.9 | 0.6 | 0.6
1–2 vessel, % | 13.1 | 9.3 | 12.9 | 7.2 | 0.07
2–3 vessel, % | 53 | 59.6 | 53.8 | 59.9 | <0.001
Left main, % | 33.1 | 31.1 | 32.4 | 32.3 | 0.05

EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure; NSTEMI = non-ST elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.
ADULT CARDIAC

inhibitors were increased in the low LVEF categories. whereas prescriptions for angiotensin-converting enzyme (ACE) inhibitors were increased in the low LVEF categories.

risk factors for death were LVEF of less than 0.35, age, chronic obstructive pulmonary disease, congestive heart failure, peripheral vascular disease, dialysis-dependent renal failure, and type 2 diabetes mellitus (Table 3). Patients amongst the groups were consistently discharged on appropriate medical therapy, including similar rates of prescription of aspirin, stains, and β-blockers, whereas prescriptions for angiotensin-converting enzyme inhibitors were increased in the low LVEF categories.

Also, there was no significant correlation between elevated LVEDP and decreased survival in patients with an LVEF > 0.35 (groups 1 vs 3). However, an elevated LVEDP was associated with significantly decreased long-term survival in patients with a depressed LVEF (group 2 vs 4, p < 0.001; Fig 1). Survival results were not significantly influenced by era bias because there were similar numbers of patients in each category throughout the study.

Other Significant Predictors of Poor Long-Term Survival

Cox proportional hazard modeling was used to analyze the entire cohort of 6,735 patients to determine independent predictors of death by entering all preoperative categoric variables and angiographic variables found in Tables 1 and 2, respectively. LVEDP and LVEF were used as categoric variables defined as LVEDP of 18 mm Hg or more and LVEF of less than 0.35. Interestingly, LVEDP of 18 mm Hg or more was not a significant independent predictor of long-term death. The significant independent risk factors for death were LVEF of less than 0.35, age, chronic obstructive pulmonary disease, congestive heart failure, peripheral vascular disease, dialysis-dependent renal failure, and type 2 diabetes mellitus (Table 3). Patients amongst the groups were consistently discharged on appropriate medical therapy, including similar rates of prescription of aspirin, stains, and β-blockers, whereas prescriptions for angiotensin-converting enzyme inhibitors were increased in the low LVEF categories.

Comment

This is the largest study to date to show that in patients with a depressed LVEF, an elevated LVEDP is significantly associated with decreased long-term survival. We show that an elevated LVEDP is not an overall independent risk factor for long-term survival after isolated CABG and is only of prognostic value in patients specifically with a depressed LVEF. A small cohort study by Pocar and colleagues [14] of 45 patients with depressed LVEF (LVEF < 0.35) showed that elevated LVEDP (n = 9) was correlated with decreased long-term survival. This study was important because it showed the value of LVEDP beyond the perioperative and 30-day period. The study by Pocar and colleagues was limited by only studying 9 patients with an elevated LVEDP compared with 4,003 patients with an elevated LVEDP in the current study.

Another recent study by Sastry and colleagues [11] has also given further prognostic value to an elevated LVEDP, showing decreased in-hospital survival in 925 patients undergoing isolated CABG. Our cohort consists of 6,735 patients, and our data support results from Sastry and colleagues because patients with an elevated LVEDP and a depressed LVEF had significantly increased 30-day mortality compared with patients without an elevated LVEDP.

The survival difference among patients with a depressed LVEF and an elevated LVEDP demonstrated by this current study advocate for the use of elevated LVEDP in predicting long-term survival for patients undergoing CABG with LV dysfunction. Unfortunately, the timing and overall intravascular volume status of patients undergoing left heart catheterization before CABG is not standardized. As such, the results of the current study represent real-world LVEDP measurements and do not imply a direct causative association between an elevated LVEDP and decreased long-term survival. Nonetheless, despite the acute transient changes in LVEDP, we show that it is a significant predictor of outcomes in patients with depressed LVEF beyond the perioperative period and up to 8 years after CABG. These results are useful to clinicians when informing patients of extended prognosis beyond in-hospital survival.

The present study further supports the predictive value of depressed LVEF in 30-day mortality as well as long-term mortality in patients undergoing isolated CABG [9]. These data are consistent with several risk-stratification studies from previous eras of CABG [10]. As well, we note that despite improved survival in

Table 3. Hazards of Death of Patients Undergoing Isolated Coronary Artery Bypass Grafting

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07 (1.05–1.08)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.84 (1.32–2.56)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2.43 (1.78–3.32)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.42 (1.01–1.20)</td>
</tr>
<tr>
<td>Dialysis dependence</td>
<td>3.96 (2.04–7.68)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.37 (1.02–1.85)</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio.
patients with a depressed LVEF undergoing isolated CABG in current practice, there continues to be a sustained and incremental long-term survival risk associated with depressed LVEF. This study clearly shows a long-term dichotomous divergence based on depressed LVEF. We also show further divergence among patients with a depressed LVEF when stratified to an elevated LVEDP. Interestingly, an elevated LVEDP lacks long-term prognostic value in patients with an LVEF exceeding 0.35.

A limitation of this study is that the data were collected in a clinical prospective registry and were observational in nature. Another limitation is that the quantification of preoperative LVEF was not standardized because echocardiography and cardiac catheterization (both calculated planimetry and visual estimation) were used in the context of usual care. Also, the use of LVEDP as a surrogate of diastolic dysfunction is less validated in the absence of LV volumes or echocardiographic evaluation of diastolic filling patterns, and hence, there are no speculative comments about the prognostic implications of long-term systolic vs diastolic dysfunction after CABG [15].

Another limitation is the use of death as the only long-term outcome for hazards modeling. Other surrogate end points, including rates of reinfarction, hospital readmission, need for further coronary intervention, and progression of symptoms, would all be valuable outcomes to measure.

The lack of catheterization after CABG to determine if a reduction in LVEDP or an improvement in LVEF occurs over time in patients with successful revascularization is a further limitation. Indeed, a LVEDP may be more sensitive in predicting improved late survival. The presence of hibernating or ischemic myocardium was also not captured for all patients; thus, we cannot correlate survival differences in patients with successful revascularization and increased postoperative LVEF compared with patients where the LVEF did not improve.

In conclusion, we have shown in patients with a depressed LVEF specifically, an elevated LVEDP is significantly associated with poor long-term survival in patients undergoing isolated CABG. However, an elevated LVEDP is not a significant risk factor for poor survival after CABG in patients with an LVEF exceeding 0.35. Further, a depressed LVEF continues to be the most significant risk factor for long-term mortality, and the addition of an elevated LVEDP provides further prognostic value to the cohort with depressed LVEF. Therefore, elevated LVEDP should be considered when assessing risk and long-term benefit derived in patients undergoing CABG with a depressed LVEF.

This work was supported by grants from the Mazankowski Alberta Heart Institute, and University of Alberta Hospital Foundation. We acknowledge Mary Ann James, Sonia Iszczenko, Leona Triplett, and Lucina Chow in the cardiovascular surgery research office for their ever-diligent work in record review and entry of data that was presented in this report.

References