

CARDIOVASCULAR

**Left ventricular end-diastolic pressure is a predictor of mortality in cardiac surgery independently of left ventricular ejection fraction**

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**Background.** Several risk factors have been shown to increase mortality in cardiac surgery. However, the importance of left ventricular end-diastolic pressure (LVEDP) as an independent risk factor before cardiac surgery is unclear.

**Method.** This observational study investigated 3024 consecutive adult patients who underwent cardiac surgical procedures at the Montreal Heart Institute from 1996 to 2000. The primary outcome was in-hospital mortality with 99 deaths (3.3%) among these patients.

**Results.** Of the 35 variables subjected to univariate analysis, 23 demonstrated a significant association with mortality. Stepwise multivariate logistic regression identified LVEDP as an independent predictor of mortality after cardiac surgery. The area under the receiver operating characteristic curve of the model predicting mortality was 0.85.

**Conclusions.** Elevated LVEDP is an independent predictor of mortality in cardiac surgery. This variable is independent of left ventricular ejection fraction.

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Several risk factors contribute to increased mortality and morbidity in cardiac surgery. These include female gender, age above 70 yr, reduced left ventricular ejection fraction (LVEF), morbid obesity, repeat surgery, type and urgency of surgery and the presence of associated diseases.<sup>1–5</sup> However, the importance of left ventricular end-diastolic pressure (LVEDP) as an independent predictor before cardiac surgery is unclear. Elevated LVEDP has been shown to correlate with worsened outcomes in cardiac surgery, but in most of these studies it has not been found to be an independent risk factor compared with LVEF,<sup>1,6</sup> and it has been investigated only in patients undergoing cardiac revascularization surgery.<sup>4</sup> In addition, elevated LVEDP may or may not be associated with systolic dysfunction, suggesting diastolic dysfunction in the absence of reduced LVEF as defined by the European Study Group on Diastolic Heart Failure.<sup>7</sup> Recently, preoperative diastolic dysfunction diagnosed using echocardiography has been linked with postoperative complications after cardiac

surgery.<sup>8–10</sup> Preoperative left ventricular diastolic dysfunction was found to be as important a predictor as systolic dysfunction.<sup>8</sup> However, the significance of this finding in a larger population is unknown. We therefore conducted an observational study to clarify the relationship between elevated preoperative LVEDP and mortality after cardiac surgery. Our hypothesis is that elevated preoperative LVEDP is an independent risk factor as important as LVEF in predicting mortality in cardiac surgery.

## Methodology

### Patients

For quality assurance purposes, the Department of Anesthesiology maintains a database on all patients undergoing cardiac surgery. This observational study included 3024 adult patients who underwent cardiac operations at the

Montreal Heart Institute from 1996 to 2000 (61% of the population operated in that period) and in whom both LVEDP and LVEF were measured before their cardiac surgery. Approval was obtained from our institutional research and ethics committees. Preoperative echocardiographic evaluation of diastolic dysfunction became available only in 1999 in our Institution. Preoperative, intraoperative and postoperative data were extracted from the hospital database. Patients who underwent coronary artery bypass grafting (CABG), valvular and other complex cardiac surgeries were included.

### Definition of preoperative data

Preoperative data were collected for the following variables: patient age and gender, body mass index, smoking history, medical treatment before surgery, recent myocardial infarction, history of hypertension, diabetes, atherosclerosis, chronic lung disease, neurological deficit, pacemaker use, LVEDP and LVEF, haemoglobin concentration, plasma creatinine concentration and cardiac medications.

Unstable angina was defined as the occurrence of documented episodes in the 6 weeks preceding surgery. Patients with crescendo angina or main left artery stenosis who were in the hospital waiting for surgery were included in this category. Congestive heart failure was reported when present or previously documented episode(s) of pulmonary congestion with or without clinical or radiological signs. Arteriosclerosis of the neck vessels was diagnosed by stenosis present in either common, internal or external carotid artery or stenosis of the vertebral artery or documented carotid bruit on physical examination. Peripheral vascular disease was determined by history of intermittent claudication or previous peripheral vascular operation or any atherosclerotic disease in all arteries except those of the neck.

LVEF was the last measured value reported before surgery by left ventriculography,<sup>11</sup> echography<sup>12</sup> or nuclear medicine.<sup>13</sup> The lowest value was selected. LVEDP was determined in the catheterization laboratory using a calibrated fluid filled system before left ventriculography. LVEDP was measured at the Z-point, which is identified on the left ventricular pressure trace as the point at which the slope of the ventricular pressure upstroke changes, approximately 50 ms after the ECG Q wave, and generally coinciding with the ECG R wave.<sup>14</sup>

Surgical procedures were categorized as CABG, valvular, complex valve, re-operations and various. The complex operations were either multivalvular or valvular with CABG. This includes ascending thoracic aorta operation and surgery for complications of myocardial infarction. Off-pump cardiac surgery and surgery of the descending aorta or patent ductus arteriosus were excluded.

The intraoperative data collected included duration of cardiopulmonary bypass, duration of aortic cross-clamping or ischaemic time, ease of weaning off cardiopulmonary

bypass defined as separation from bypass without vasoactive drugs or intra-aortic balloon pump and blood loss.

### Outcomes

The primary outcome in this study was in-hospital mortality. Patients undergoing CABG were further stratified according to abnormal left ventricular function, determined by either LVEF below 30% or LVEDP exceeding 19 mm Hg. Those LVEF and LVEDP values were based on previous studies which identified them as cut-offs associated with increased mortality and morbidity.<sup>5,6,15</sup>

### Statistical analysis

The results are expressed as mean (SD) for continuous variables or as percentages for categorical variables. Univariate analyses (*t*-test for continuous variables and the Pearson  $\chi^2$ -test for categorical variables) were used to establish which perioperative variables were related to death. Only variables with *P*-values <0.25 in univariate analysis were considered as potential predictors of the primary outcome for multivariate analysis. Variable clustering was employed to further reduce the number of redundant variables before building a multivariate model. Then, multiple stepwise logistic regression analysis was undertaken to determine the independent predictors of death. *P*-values <0.05 were considered to be statistically significant.

To address the question of model stability and, more precisely, to assess the importance of including LVEDP in a model predicting mortality, a bootstrap re-sampling procedure with stepwise selection of variables in each replication was carried out.<sup>16</sup>

Five thousand (5000) bootstrap samples of 3419 size were drawn with replacement. Stepwise logistic regression of all the clinically relevant variables described previously was performed in the original sample. The same statistical approach was applied in each replication with the aim of determining whether LVEDP would be selected or not in the bootstrap samples. The results are presented as percentages of selection of LVEDP, that is, the number of times that LVEDP was selected in the model out of the 5000 bootstrap samples.

### Results

A total of 3024 patients were studied. There were 99 deaths (3.3%). Patient characteristics for mortality are reported in Table 1. Of the 99 deaths, 57% were attributed to haemodynamic instability or surgical complications, 23% to sepsis, 8.5% to respiratory problems, 3% to neurological causes, and 8.5% to miscellaneous causes. The mean length of stay in the intensive care unit including step down unit and in the hospital was, respectively, 4 and 8 days for survivors. A total of 287 (9%) patients experienced a length of stay of 2 weeks or more.

**Table 1** Preoperative variables and mortality. LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; CPB, cardiopulmonary bypass; TIA, transient ischaemic attack; ACE, angiotensin-converting enzyme. †Age, weight, height, BMI, LVEF, LVEDP, haemoglobin, creatinine, cardiopulmonary bypass duration and aortic cross-clamp duration are means (range or SD). \*Transient ischaemic attack

Preoperative variables	Survivors (n=2925)	Deceased (n=99)	P-value
Age†	63 (53–73)	68 (58–78)	<0.0001
Weight (kg)†	75 (15)	70 (16)	0.0003
Height (cm)†	165 (9)	162 (10)	<0.0001
BMI (kg m <sup>-2</sup> )†	27 (5)	27 (5)	0.205
LVEF†	55 (14)	47 (16)	<0.0001
LVEF (angiography) (n=2282)	58 (13)	47 (14)	<0.0001
LVEF (other) (n=709)	51 (16)	40 (15)	<0.0001
LVEDP† preangiography	20 (8)	23 (9)	0.0019
Haemoglobin (g dl <sup>-1</sup> )†	13.7 (1.6)	12.7 (1.7)	<0.0001
Creatinine (µmol litre <sup>-1</sup> )†	104 (32)	126 (56)	0.0002
CPB duration (min)†	83 (34)	131 (72)	<0.0001
Aortic cross-clamp duration (min)†	55 (45)	71 (44)	0.0007
Female gender	28%	41%	0.0025
Recent myocardial infarction	15%	21%	0.0930
Congestive heart failure			<0.0001
Types of surgery	29%	68%	<0.0001
Revascularization	2076 (71%)	53 (54%)	
Complex revascularization	252 (8.6%)	20 (20%)	
Aortic valve replacement	272 (9.3%)	5 (5%)	
Mitral valve replacement	156 (5.3%)	5 (5%)	
Complex valve surgery	118 (4%)	10 (10%)	
Various	51 (1.7%)	6 (6%)	
Re-operation	12%	32%	<0.0001
Hypertension	45%	55%	0.0550
Atherosclerosis	19%	26%	0.0673
Carotid atherosclerosis	10%	18%	0.0093
Peripheral atherosclerosis	13%	18%	0.1081
History of vascular surgery	5%	10%	0.0386
History of stroke or TIA*	7%	11%	0.0939
Smoker	26%	21%	0.2787
History of pulmonary disease	9%	19%	0.0003
Treated diabetes	18%	27%	0.0255
Neurological deficit	2%	1%	0.4327
β-blockers	59%	54%	0.2470
Calcium channel blockers	45%	49%	0.4019
ACE inhibitors	29%	36%	0.1277
Digitalis	14%	21%	0.0294
Diuretics	30%	53%	<0.0001
Antiarrhythmic agents	7%	10%	0.2777
Nitrates i.v.	26%	40%	0.0012
Atrial fibrillation	11%	19%	0.0133
Vasopressors	1%	6%	<0.0001
Intra-aortic balloon pump	4%	17%	<0.0001

Of the 35 variables subjected to univariate analysis, 23 demonstrated a significant association with the occurrence of death. Multiple stepwise logistic regression identified eight variables to be independent predictors of death after cardiac surgery (Table 2). These were age, weight, hypertension, treated diabetes, re-operation, LVEDP, LVEF and duration of cardiopulmonary bypass. The area under the receiver operating characteristic (ROC) curve was 0.85 for the prediction of mortality. The LVEDP independently predicted mortality [ $P=0.0062$ , odds ratio (OR) of 1.19 (95% confidence interval (CI) 1.05–1.35].

Among patients undergoing only coronary revascularization ( $n=2445$ ) and stratified by LVEDP  $\leq$  or  $>19$  mm Hg and LVEF  $<$  or  $\geq 30\%$ , no death was observed in the group

**Table 2** Multivariate analysis: mortality. CI, confidence interval; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass

Predictors	P-value	Units	Odds ratio	95% CI
Age	<0.0001	20	4.255	2.461–7.355
Weight (kg)	0.0403	–10	1.190	1.008–1.404
LVEDP	0.0062	5	1.195	1.052–1.357
LVEF	0.0002	–10	1.326	1.145–1.535
CPB duration (min)	<0.0001	30	1.813	1.608–2.044
Re-operation	<0.0001	–	2.669	1.636–4.354
Hypertension	0.0211	–	1.687	1.082–2.632
Treated diabetes	0.0277	–	1.759	1.064–2.906

**Table 3** Death in 2445 patients undergoing CABG. LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction. \* $P<0.0001$  compared with patients with LVEDP  $\leq 19$  and LVEF  $< 30$

Death	LVEDP >19 mm Hg LVEF<30%	LVEDP >19 mm Hg LVEF $\geq 30\%$	LVEDP $\leq 19$ mm Hg LVEF<30%	LVEDP $\leq 19$ mm Hg LVEF $\geq 30\%$
No	75 (88%)	1244 (97%)	30 (100%)	1033 (98%)
Yes	10 (12%)*	35 (3%)	0 (0%)	18 (2%)
Total	85	1,279	30	1,051

**Table 4** Death in 895 patients undergoing non-CABG. LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction

Death	LVEDP >19 mm Hg LVEF<30%	LVEDP >19 mm Hg LVEF $\geq 30\%$	LVEDP $\leq 19$ mm Hg LVEF<30%	LVEDP $\leq 19$ mm Hg LVEF $\geq 30\%$
No	41 (89%)	292 (94%)	26 (93%)	480 (96%)
Yes	5 (11%)	19 (6%)	2 (7%)	20 (4%)
Total	46	311	28	500

with low LVEF and low LVEDP as opposed to 10 deaths (12%) in the group with low LVEF and elevated LVEDP ( $P<0.0001$ ) (Table 3). Among patients undergoing only non-coronary revascularization ( $n=895$ ) and stratified by LVEDP  $\leq$  or  $>19$  mm Hg and LVEF  $<$  or  $\geq 30\%$ , two deaths (7%) were observed in the group with low LVEF and low LVEDP ( $n=28$ ) as opposed to five (11%) deaths in the group with low LVEF and elevated LVEDP ( $n=46$ ) ( $P=0.1475$ ) (Table 4).

In the analysis of mortality, logistic regression was performed in the 5000 bootstrap samples, and LVEDP was included in the model at a 0.05 significance level in 3662 (73.23%) replications. This suggests that LVEDP should be selected as a predictor of mortality in addition to LVEF and type of cardiac surgery.

## Discussion

This study reveals that elevated LVEDP is an independent predictor of death after cardiac surgery independently of LVEF. This is consistent with the hypothesis that elevated LVEDP could be associated with systolic but also diastolic

dysfunction which is a known prognostic factor.<sup>17–21</sup> In addition, it supports the recent echocardiographic observation that preoperative diastolic dysfunction predisposes to postoperative complications.<sup>8–10</sup>

Several worldwide studies have identified predictors of mortality and morbidity after cardiac surgery over the last decade,<sup>2,4,5,15,22–25</sup> but few of them have underscored the importance of LVEDP.

O'Connor and colleagues<sup>4</sup> in a 1992 prospective regional trial enrolled 3055 patients undergoing isolated CABG. Their in-hospital mortality rate was 4.3%, and they found that patients with LVEDP >22 mm Hg had approximately a 2-fold increase in the risk of mortality (OR 2.1;  $P=0.005$ ) compared with those with LVEDP  $\leq$ 14 mm Hg. The ROC of their model was 0.76, using gender, age, LVEDP, ejection fraction, co-morbidity, re-operation and body surface area. The characteristics of the O'Connor study population could not be compared with ours because their details were not reported. However, LVEDP was measured in only 77.8% of their cohort; they excluded non-CABG patients, and post-operative complications in relation to LVEDP were not included. In our model, 30% of our population underwent non-revascularization surgery.

Elevated LVEDP could predispose to mortality after cardiac surgery for several reasons. First, it is commonly associated with reduced left ventricular function which is a well-known risk factor for mortality.<sup>2,4,5,15,22–26</sup> Second, one frequent cause of elevated LVEDP is left ventricular hypertrophy, a risk factor for diastolic dysfunction<sup>27</sup> and a known surgical risk factor in congenital surgery<sup>28</sup> secondary to inadequate myocardial protection. The presence of left ventricular hypertrophy will be associated with increased dependence on glycolysis for energy production and altered calcium regulation for excitation–contraction coupling.<sup>29</sup> In this study, measurements of left ventricular hypertrophy or mass were not reported. However, hypertension which is commonly associated with left ventricular hypertrophy was found to be an independent predictor of mortality.

Third, it is possible that patients with normal systolic function and elevated LVEDP are at higher risk of mortality after cardiac surgery because of the deleterious effect of elevated LVEDP with associated filling abnormalities. These abnormal loading conditions may render the patient very sensitive to perioperative, often abrupt changes in loading conditions with hypovolaemia on one hand and volume overload on the other. This situation is typical of diastolic dysfunction. Redfield and colleagues<sup>21</sup> in a study of 2042 randomly selected patients demonstrated that the presence of even mild diastolic dysfunction reduces long-term survival.

Finally, patients with elevated LVEDP could have associated secondary pulmonary hypertension,<sup>30</sup> a variable linked with increased morbidity and mortality in cardiac surgery.<sup>5,15,22,30,31</sup> In a study of 41 patients with severe reduction in LVEF, Maslow and colleagues<sup>32</sup> observed that all the patients with associated reduced right ventricular

dysfunction died within 2 yr of cardiac surgery. In this group, the mean pulmonary artery pressure was higher and restrictive left ventricular diastolic dysfunction (the more severe type) more common in patients with right ventricular dysfunction. Although the LVEDP was not measured, severe left ventricular diastolic dysfunction is associated with elevated LVEDP.

## Limitations

This study has several limitations. First, our cohort was selected from a group of patients in whom LVEF and LVEDP measurements were available, and the decision to measure LVEDP was left to the cardiologist. Consequently, during diagnostic cardiac catheterization a selection bias could be introduced as LVEDP has been measured in a specific population. However, it was available in 61% of the population operated in that period. Despite the fact that patients with high LVEDP and normal LVEF could have diastolic dysfunction,<sup>7</sup> these are crude measurements and cannot be as accurate as echocardiographic criteria in the evaluation of diastolic function. Preoperative echocardiographic evaluation of diastolic dysfunction was, however, not available in that population. We also did not exclude patients undergoing non-revascularization surgery. Echocardiographic measurements used in the evaluation of diastolic dysfunction are frequently not performed in patients with valvular heart disease, and these data were not available in our patients. However, we found that elevated LVEDP remained statistically significant independent of the type of surgical procedure. Several studies have also shown that abnormal diastolic patterns in valvular dysfunction, such as in mitral and aortic insufficiency, are used in severity stratification.<sup>33</sup> The measurement of LVEF is dependent on contractility and afterload but its value is relatively constant in steady-state preload conditions.<sup>34</sup> In our study, it was obtained through angiography in 75% of our patients because LVEDP was measured simultaneously. Therefore the timing was different in those in whom LVEF was obtained through another method. However, several studies have shown a good correlation between the different technique of LVEF measurement.<sup>13,35</sup> Finally the surgical procedures were also performed by eight surgeons and nine anaesthetists from a single institution. All these factors which have not been controlled in previous studies, however, would require to be addressed in future multicentred trials on the importance of preoperative diastolic dysfunction in cardiac surgery.

## Conclusion

In summary, elevated LVEDP is an independent risk factor of mortality in cardiac surgery. Future studies should explore the importance of preoperative diastolic dysfunction and the clinical implication for the anaesthetist.

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