Effect of diastolic dysfunction on postoperative outcomes after cardiovascular surgery: A systematic review and meta-analysis

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ABSTRACT

Objective: The objective of this study was to investigate the effect of preoperative diastolic dysfunction on postoperative mortality and morbidity after cardiovascular surgery.

Methods: We systematically searched for articles that assessed the prognostic role of diastolic dysfunction on cardiovascular surgery in PubMed, Cochrane Library, Web of Science, Embase, and Scopus until February 2016. Twelve studies (n = 8224) met our inclusion criteria. Because of the scarcity of outcome events, fixed-effects meta-analysis was performed via the Mantel-Haenszel method.

Results: Preoperative diagnosis of diastolic dysfunction was associated with greater postoperative mortality (odds ratio [OR], 2.41; 95% confidence interval [CI], 1.54–3.71; $P < .0001$), major adverse cardiac events (OR, 2.07; 95% CI, 1.55–2.78; $P \leq .0001$), and prolonged mechanical ventilation (OR, 2.08; 95% CI, 1.04–4.16; $P = .04$) compared with patients without diastolic dysfunction among patients who underwent cardiovascular surgery. The odds of postoperative myocardial infarction (OR, 1.29; 95% CI, 0.82–2.05; $P = .28$) and atrial fibrillation (OR, 2.67; 95% CI, 0.49–14.43; $P = .25$) did not significantly differ between the 2 groups. Severity of preoperative diastolic dysfunction was associated with increased postoperative mortality (OR, 21.22; 95% CI, 3.74–120.33; $P = .0006$) for Grade 3 diastolic dysfunction compared with patients with normal diastolic function. Inclusion of left ventricular ejection fraction (LVEF) $<40\%$ accompanying diastolic dysfunction did not further impact postoperative mortality ($P = .27$; $I^2 = 18\%$) compared with patients with normal LVEF and diastolic dysfunction.

Conclusions: Presence of preoperative diastolic dysfunction was associated with greater postoperative mortality and major adverse cardiac events, regardless of LVEF. Mortality was significantly greater in grade III diastolic dysfunction. (J Thorac Cardiovasc Surg 2016;152:1142–53)

One in seven patients suffer a major complication or death after coronary artery bypass surgery (CABG), and the currently available cardiac surgery risk scores do not always

correctly predict these risks.^{1–5} Recent literature emphasizes the adverse prognostic impact of diastolic dysfunction on postoperative outcomes, and many recent

Postoperative mortality after cardiovascular surgery and grade III of diastolic dysfunction.

Central Message

Grade III diastolic dysfunction is associated with greater postoperative death after cardiovascular surgery, regardless of left ventricular ejection fraction.

Perspective

Underpowered studies and heterogeneity in measurement underestimate diastolic dysfunction (DD) in the perioperative period. We show increased perioperative mortality with greater grade of DD. This is not correctly predicted by current risk scoring systems. Limitations in understanding of DD and lack of specific therapy should not discourage its preoperative staging or preventive risk stratification.

See Editorial Commentary page 1154.

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Abbreviations and Acronyms

AF	= atrial fibrillation
CABG	= coronary artery bypass surgery
CAD	= coronary artery disease
EuroSCORE	= European System for Cardiac Operative Risk Evaluation
LVEF	= left ventricular ejection fraction
MACE	= major adverse cardiac events
MI	= myocardial infarction
NOS	= Newcastle Ottawa Scale

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studies consistently rate severe diastolic dysfunction as the single most important determinant of postoperative outcome after cardiac surgery. Despite continuing controversies in the evaluation of diastolic dysfunction, recent advances in echocardiography have resulted in better assessment and reporting of diastolic dysfunction. The American College of Cardiology/American Heart Association/American Society of Echocardiography Appropriateness Criteria provide recommendations for echocardiography before noncardiac surgery but do not address the need for routine echocardiography before CABG. Among the echocardiographic criteria for risk scoring, the Society of Thoracic Surgeons uses left ventricular ejection fraction (LVEF) and significant valvular regurgitation/stenosis, whereas the European System for Cardiac Operative Risk Evaluation (EuroSCORE) includes LVEF and pulmonary arterial hypertension.

The current literature reporting postoperative outcomes after cardiac surgery in patients with varying degrees of diastolic dysfunction does not report postoperative mortality consistently as an independent outcome. Some of the reasons surrounding this observation could be mainly observational studies with low sample size or rare mortality outcomes that therefore had to be reported as part of a composite outcome of major adverse cardiac events. In addition, despite the increasing prevalence of diastolic heart failure, the majority of these patients do not happen to have severe or stage III diastolic dysfunction, thereby making it harder to assess its impact on postoperative outcomes.

We propose that diastolic dysfunction—especially if severe—can be an important predictor of postoperative

outcomes and should be considered preoperatively for better risk stratification. To better evaluate postoperative outcomes after cardiovascular surgery, we conducted a systematic review and meta-analysis to investigate the effect of preoperative diagnosis of diastolic dysfunction on postoperative mortality and morbidity.

METHODS

We conducted a systematic review following the PRISMA (ie, Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines.⁶

Search Strategy, Eligibility Criteria, and Study Selection

Two authors independently identified the relevant articles by searching the following databases: PubMed, Cochrane Library, Web of Science, EMBASE, and Scopus until February 2016. The following search terminologies were used: (coronary artery bypass graft or CABG or cardiopulmonary bypass) and (diastolic function or diastolic dysfunction or impaired relaxation or pseudo normal filling or restrictive filling or diastolic filling or LV filling pressure or E/e or tissue Doppler) and (mortality or outcome). The search strategy for PubMed is available as an Online Data Supplement. The inclusion criteria were diastolic dysfunction on postoperative outcomes, including mortality and complications after cardiac surgery. Disagreements between these 2 authors were reviewed together and the decision was made on agreement. The 2 authors independently reviewed full text articles to determine whether the study can be included for the meta-analysis. We also reviewed the references of included articles.

Data Extraction and Quality Assessment

Two authors independently extracted relevant data from the studies on the standard data extraction sheet. Extracted data included definition of diastolic dysfunction, degree of diastolic dysfunction, type of surgery, exclusion criteria, primary and secondary outcomes, mode of echocardiogram, and follow-up period.

Study Outcomes

The primary study outcome was mortality. Secondary study outcomes were postoperative complications, which include major adverse cardiac events (MACE), prolonged mechanical ventilation, atrial fibrillation (AF), and myocardial infarction (MI).

Statistical Analysis

We performed meta-analysis with RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark) and R 3.0.1 (www.r-project.org) using the Mantel-Haenszel fixed-effects model, given the scarcity of events.⁷ Random effects meta-analyses via the inverse variance method were performed otherwise. As sensitivity analyses for main analyses of mortality, 3 other methods were used: (1) natural weighting in random effects meta-analysis⁸; (2) Hartung-Knapp-Sidik-Jonkman method in random effects meta-analysis⁹; and (3) arcsine transformation of risk difference.¹⁰ For mortality, funnel plots were used to evaluate small study effects, and the Egger test was used to evaluate asymmetry of funnel plots. The Cochran χ^2 test and the I^2 test were used to assess between-study heterogeneity. Heterogeneity was considered statistically significant at $P < .1$, and substantial heterogeneity was defined as $I^2 > 50\%$. Pooled odds ratios (ORs) were reported with 95% confidence intervals (CIs).

FIGURE 1. Study selection flow chart.

Risk of Bias Evaluation

Risk of bias of cohort studies was evaluated with the Newcastle Ottawa Scale (NOS).¹¹ NOS scale evaluates the following criteria: (1) Selection: representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study; (2) Comparability: comparability of cohorts on the basis of the design or analysis; and (3) Outcome: assessment of outcome; if the follow-up was follow-up long enough for outcomes to occur; adequacy of follow-up of cohorts. The NOS assessment was done per each cohort study and awarded with stars (1-4) for each of the 3 criteria (selection, comparability, outcomes). NOS scores >7 were considered high-quality studies, and NOS scores of 5-7 were considered moderate-quality studies. We also described when available, matching variables and confounders adjusted for per study; finally, we compared, when available, unadjusted and adjusted risks per outcome and study.

RESULTS

Search Results

A total of 838 articles were retrieved after excluding mutual inclusions; 651 articles from PubMed, 92 articles from Cochrane Library, 335 articles from Web of Science, 247 articles from Embase, and 65 articles from Scopus. The algorithm for the search strategy is summarized in Figure 1. After a complete review of the articles, 8 studies were selected for the analysis and 21 studies were excluded for the following reasons: diastolic dysfunction indices not

available for 5 studies, abstract presented at conferences for 4 studies, postoperative outcomes of interest not reported for 10 studies, normal diastolic function not used for comparison in 1 study, and 1 review article. Five more studies were found eligible after references of the selected studies were reviewed,¹²⁻¹⁶ of which 1 could not be used for lack of requisite data.¹²

Description of Studies

The majority of patients were male, their mean age was 64.5 years, and most of them underwent CABG. Three studies reported patients exclusively undergoing off-pump CABG,^{14,17,18} and 1 study had patients undergoing exclusive aortic or peripheral vascular surgery.¹⁵ Preoperative diastolic dysfunction was assessed by transthoracic echocardiography,^{13,17-23} transesophageal echocardiography,^{15,24} and left heart catheterization.^{14,16} Mean follow-up ranged between inpatient postoperative period to 3.2 years (Table 1). Postoperative outcomes and confounding variables per study are described in Table 2.

Risk of Bias of Included Studies

Key points of risk of bias were assessed with the NOS (Table 3). All studies clearly identified and excluded the conditions that would be considered as important

confounders in measurement of diastolic dysfunction (Table 2). Overall, all studies clearly identified the study population, reported the main outcome, and scored well on other quality items. No selective loss of follow-up was reported. A summary of unadjusted and adjusted outcome risk estimates by presence or grade of diastolic dysfunction and per study are reported in Table E1. All studies were observational; we did not identify any trials. Our analyses provided no indication of publication bias. No asymmetry of funnel plot was noted (Figure E1), and the formal test of asymmetry was not significant (Egger test, $P = .3$).

Effect of Diastolic Dysfunction on Postoperative Mortality and MACE

A total of 10 studies ($n = 6911$)^{13-20,23,24} investigated the impact of preoperative diastolic dysfunction on postoperative mortality independent of other complications. Six studies^{13-16,19,24} reported postoperative or in-hospital mortality, 2 studies^{17,20} reported mortality up to 30 days, 1 study reported mortality from 30 days to 1 year,¹⁸ and another 1 up to 23 months.²³ To stay consistent that only postoperative outcomes were reported, we only used the 30-day data reported in the study by Lee and colleagues¹⁸ and also analyzed mortality by excluding the study by Liu and colleagues.²³ A total of 51.3% (3546/6911) of patients had diastolic dysfunction. Eighty-seven (2.45%) patients died among the 3546 patients with diastolic heart failure compared with 43 (1.28%) deaths among 3365 patients with normal diastolic function (Table 2). Preoperative diagnosis of diastolic dysfunction was associated with increased postoperative mortality after cardiac surgery (OR, 2.41; 95% CI, 1.57-3.71; $P < .001$; $I^2 = 0$) (Figure 2). Exclusion of the study by Liu and colleagues²³ did not change the overall results ($P < .0001$). The results of sensitivity analysis with the arcsine transformed risk difference (at risk difference 0.0625; 95% CI, 0.0326-0.0915; $P = .001$) were concordant with the results from the main analysis; risk difference 0.0647; 95% CI, 0.0324-0.0971; $P < .001$ when the paper by Liu and colleagues was excluded.

We also investigated the effect of severity of diastolic dysfunction on postoperative mortality. Of the studies reporting postoperative mortality, only 3 studies^{17,20,23} provided complete gradation of diastolic dysfunction and comparisons with normal diastolic function. Two studies^{13,19} used stage I diastolic dysfunction patients only for comparison with those with normal diastolic function. Of a total of 1424 patients with any degree of diastolic dysfunction, 62 (4.35%) had severe diastolic dysfunction or restrictive filling. Greater postoperative mortality was noted with increasing severity of diastolic dysfunction, but it was statistically significant only in the group with severe diastolic dysfunction or restrictive filling (OR, 21.22; 95% CI, 3.74-120.33; $P = .006$;

$I^2 = 0$) (Figure 3). Percentage mortality was 1.12% in delayed relaxation phase; 2.39% in pseudo-normal filling, and 16% in restrictive filling group. Exclusion of the paper by Liu and colleagues²³ did not change the overall results, $Z = 2.93$ ($P = .003$).

Diastolic dysfunction on preoperative echocardiogram was associated with a greater incidence of MACE (OR, 2.07; 95% CI, 1.55-2.78; $P < .0001$) and prolonged mechanical ventilation (OR, 2.08; 95% CI, 1.04-4.16; $P = .04$) (Figure 4) among patients who underwent cardiac surgery. Youn and colleagues¹⁷ and Lee and colleagues¹⁸ reported both postoperative mortality and MACE and death was included in MACE; however, diastolic dysfunction continued to be associated with MACE after these studies were excluded in a sensitivity analysis (OR, 1.94; 95% CI, 1.32-2.86; $P = .0007$; $I^2 = 0$) (Figure E2). The severity of diastolic dysfunction also was associated with a greater incidence of MACE but was statistically significant only in grade II (OR, 1.84; 95% CI, 0.99-3.43; $P = .05$; $I^2 = 0$) and grade III severity classes (OR, 4.69; 95% CI, 2.52-8.72; $P < .0001$) (Figure E3). Postoperative MI and AF did not differ between the 2 groups (Figure 4).

Subgroup Analyses

The following subgroups were analyzed: patients with diastolic dysfunction with normal LVEF or mean LVEF > 40 versus patients with diastolic dysfunction with LVEF < 40 ; types of cardiac surgery (CABG + valve vs CABG only), and diastolic dysfunction as reported by transthoracic echocardiography or transesophageal echocardiography. The excess in postoperative mortality associated with diastolic function was noted in both the groups that included patients with normal LVEF as well as with reduced LVEF (OR, 2.16; 95% CI, 1.35-3.45 vs OR, 4.31; 95% CI, 1.39-13.38; P for interaction = .27; $I^2 = 17.8\%$; Figure E4). Postoperative outcomes were similar regardless of whether diastolic dysfunction was identified and quantified by transthoracic (OR, 2.42; 95% CI, 1.54-3.80) versus transesophageal echocardiogram (OR, 2.34; 95% CI, 0.56-9.79); P for interaction = .97; $I^2 = 0\%$ (Figure E5) or by the type of surgery: CABG, OR 2.42, 95% CI 1.54-3.80 versus CABG + valve surgery, OR 12.57, 95% CI 0.58-274.49 versus vascular surgery, OR 1.20, 95% CI 0.21-6.70; P for interaction = .42; $I^2 = 0\%$ (Figure E6). Subgroup analysis for outcomes by age was not possible.

DISCUSSION

Within the limitations associated with assessing the true impact of diastolic dysfunction on perioperative outcomes after cardiovascular surgery, our analysis reveals greater postoperative mortality in patients with diastolic dysfunction. In a subgroup analysis, this effect was seen

TABLE 1. Characteristics of included studies

First author, year of publication	Type of surgery	Sample size	Age, y mean (SD)	Males (%)	BMI, mean (SD)	Obesity, %	HTN, %	Diabetes, %
Afilalo, 2013	CABG	No DD: 237 DD: 395	67.2 (11.1)	77.2	28.8 (5.2)	NS	NS	37.5
Bagheri, 2010	CABG	No DD: 361 DD: 27	No DD: 57.7 (9.5) DD: 61.2 (9.5)	68.0	NS	NS	No DD: 45.2 DD: 40.7	No DD: 23.1 DD: 29.6
Bernard, 2001	On-pump CABG (78.8%); combined procedures, valvular surgery and reoperations (21.2%)	No DD: 46 DD: 20	No DD: 63 (8) DD: 67 (8)	66.7	No DD: 27.3 DD: 25.3	NS	No DD: 47.8 DD: 55.0	No DD: 19.6 DD: 40.0
Değirmencioglu, 2013	CABG	No DD: 168 DD: 304	No DD: 58.1 (0.8) DD: 62.4 (0.5)	75.6	No DD: 29.1 (4.3) DD: 29.1 (4.4)	NS	No DD: 71.4 DD: 80.6	No DD: 35.1 DD: 42.9
Lee, 2012	Off-pump CABG	No DD: 744 DD: 304	No DD: 63 DD: 67	75.4	No DD: 24.6 (2.7) DD: 24.9 (3.0)	NS	No DD: 58.9 DD: 74.3	No DD: 40.2 DD: 62.2
Liu, 2003	CABG	No DD: 37 DD: 65	No DD: 66 (9) DD: 66.1 (8.7)	74.5	NS	NS	No DD: 35.0 DD: 36.9	No DD: 38.0 DD: 41.5
Matyal, 2009	Elective vascular surgery (aortic or peripheral)	No DD: 80 DD: 134	70.8	63.0	NS	NS	85.0	76.2
Melduni, 2011	CABG (45.6%); valvular surgery, and CABG + valvular surgery (54.4%)	No DD: 79 DD: 272	66.7 (13.6)	67.2	28.2 (5.2)	NS	74.1	25.9
Merello, 2008	On-pump CABG	No DD: 33 DD: 158	No DD: 59.1 (9.4) DD: 63.9 (8.6)	72.3	No DD: 27.4 DD: 26.7	No DD: 12.1 DD: 13.9	No DD: 69.7 DD: 81.0	No DD: 33.3 DD: 32.9
Salem, 2006	CABG (87.1%); valvular surgery, and CABG + valvular surgery (12.9%)	No DD: 1051 DD: 1279	63.2	63.3	27 (5)	NS	45.3	18.3
Sastry, 2010	Off-pump CABG	No DD: 790 DD: 54	No DD: 64.7 DD: 66.2	80.0	No DD: 28.2 DD: 28.2	NS	No DD: 57.6 DD: 57.4	No DD: 21.3 DD: 22.2
Youn, 2011	Off-pump CABG	No DD: 55 DD: 1201	No DD: 54.9 (9.9) DD: 63.5 (8.4)	71.8	NS	No DD: 5.5 DD: 2.8	No DD: 43.6 DD: 66.5	No DD: 20.0 DD: 42.5

SD, Standard deviation; BMI, body mass index; HTN, hypertension; LVEF, left ventricular ejection fraction; Y, yes; N, no; CABG, coronary artery bypass graft; DD, diastolic dysfunction; NS, not stated; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; CPB, cardiopulmonary bypass; AF, atrial fibrillation; bpm, beats per minute; ICU, intensive care unit; MR, mitral regurgitation; MI, myocardial infarction; CHF, congestive heart failure; CHD, congenital heart disease; LVEDP, left ventricular end-diastolic pressure; PDA, patent ductus arteriosus; CBP, cardiopulmonary bypass; TDI, tissue Doppler imaging. *Mean (standard deviation).

TABLE 1. Continued

Preoperative diastolic dysfunction indices measured by	Follow-up period	Study enrolled normal LVEF patients only (Y/N)	Study exclusion criteria	Primary outcome(s)
TTE	3.2 y	N	Echocardiographic reports from an outside center; digital echocardiographic images not retrievable because of technical reasons	In-hospital mortality or major morbidity
Echocardiography	Postoperative	Y	LVEF <50%; CABG with valve surgery or AF ablation therapy	NS
TEE	Postoperative	N	Cardiac surgery without CPB; heart rate more than 100 bpm; persistent arrhythmia; if they required a pacemaker	Mortality and surgical ICU length of stay
Mitral inflow waves, tissue Doppler imaging and pulmonary vein flow analysis by echocardiography	30 d	Y	LVEF <50%; baseline rhythm other than sinus; moderate or severe valvular dysfunction; moderate or severe diastolic dysfunction	Perioperative morbidity and mortality
TTE	1 y	N	AF; emergency surgery; concomitant valvular or aortic surgery; participation in another trial during that period; grade $\geq 2/4$ MR on echocardiography; those with a preoperative inotrope, intra-aortic balloon pump or ventricular assist device support	Major adverse cardiac events
Trans-mitral flow, pulmonary venous flow by Doppler echocardiography	29 (20) mo*	N	AF; sinus tachycardia; valvular aortic stenosis; emergency operation for acute MI; grade $>2/4$ MR; chronic renal failure	Cardiac events
TEE	Postoperative	N	Emergency surgery, surgery under regional anesthesia; severe vascular disorders; contraindications to TEE	MI, CHF, significant arrhythmia, prolonged intubation, renal failure, and death
TTE	30 d	N	History of AF, Cox maze, or radiofrequency ablation procedure for atrial arrhythmias; CHD; moderate or severe mitral stenosis; incomplete diastolic function assessment	Postoperative AF
Pulsed Doppler mitral filling flow, left ventricular diastolic filling patterns measured by echocardiography	30 d	N	AF; off-pump CABG; CABG associated with valve surgery; severe mitral or aortic valvulopathy; implanted pacemaker	Postoperative morbidity and mortality
LVEDP	Postoperative	N	Off-pump CABG; surgery of the descending aorta or PDA	In-hospital mortality
LVEDP	Postoperative	N	Revascularization on CBP	In-hospital mortality and ICU length of stay
TTE	30 d	N	AF; grade more than $2/4$ MR; need for dialysis; urgent/emergency operation; undetermined diastolic function including sinus tachycardia; aortic stenosis; on-pump conversion; diastolic function not assessed by TDI	Major adverse cardiac events

TABLE 2. Confounding variables identified and postoperative outcomes

First author, year of publication	Diastolic dysfunction	Sample size	Matching	Identified confounding variables	Mortality		MACE		MI	AF	Prolonged mechanical ventilation
					Definition	n (%)	Definition	n (%)	n (%)	n (%)	n (%)
Afilalo, 2013	No	237	No	RV systolic dysfunction, RV inefficiency (myocardial performance index), mitral regurgitation	NA		26 (11.0) 71 (18.0)		NA	NA	NA
	Yes	395									
Bagheri, 2010	No	361	No	No	Postoperative mortality	8 (0.2)	NA	4 (1.1) 0	NA	NA	23 (6.4) 4 (14.8)
	Yes	27				2 (7.4)					
Bernard, 2001	No	46	No	No	Postoperative mortality	0	NA	NA	NA	NA	NA
	Yes	20				2 (10.0)					
Degirmencioglu, 2013	No	168	No	No	Postoperative mortality	0	NA	NA	17 (1.0) 34 (11.2)	NA	NA
	Yes	304				5 (1.6)					
Lee, 2012	No	744	No	LVEF, BMI, left main disease, smoking, preoperative beta- blocker, number of grafted vessels, operation time	30-d/1-y mortality	3 (4.1)/10 (1.3)	NA	NA	NA	NA	NA
	Yes	304				8 (2.6)/11 (3.6)					
Liu, 2003	No	37	No	Age, sex, LVEF, multivessel disease, left main disease, pump time, history of CVD	29 ± 20 mo mortality	0	NA	1 (2.7) 0	NA	NA	NA
	Yes	65				3 (4.6)					
Matyal, 2009	No	80	No	Surgery, age, renal failure, female, history of stroke, DM, and LVEF	Postoperative mortality	2 (25.0)	17 (21.3) 77 (57.5)	5 (6.3) 8 (6.0)	NA	NA	4 (5.0) 11 (8.2)
	Yes	134				4 (3.0)					
Melduni, 2011	No	79	No	Age, BMI, hypertension, mitral regurgitation, univalvular vs multivalvular surgery, CABG + valvular surgery, perfusion time	NA	NA	NA	NA	4 (5.1) 131 (48.2)	NA	NA
	Yes	272									
Merello, 2008	No	33	No	Age and renal failure	30-d mortality	0	9 (27.3) 56 (35.4)	1 (3.0) 7 (4.4)	5 (15.2) 25 (15.8)	0	14 (0.6)
	Yes	158				13 (8.2)					
Salem, 2006	No	1051	No	Age, weight, LVEF, CPB duration, reoperation, hypertension, treated DM	In-hospital mortality	18 (1.7)	NA	NA	NA	NA	NA
	Yes	1279				35 (2.7)					
Sastry, 2010	No	790	No	EuroSCORE	In-hospital mortality	12 (1.5)	NA	NA	NA	NA	NA
	Yes	54				3 (5.6)					
Youn, 2011	No	55	No	Renal failure, EuroSCORE >5, 3-vessel disease, LVEF <35%	30-d mortality	0	1 (1.8) 49 (4.1)	1 (1.8) 37 (3.1)	NA	NA	2 (3.6) 65 (5.4)
	Yes	1201				12 (1.0)					

MACE, Major adverse cardiovascular events; MI, myocardial infarction; AF, atrial fibrillation; RV, right ventricle; NA, not available; LVEF, left ventricular ejection fraction; BMI, body mass index; CVD, cerebrovascular disease; DM, diabetes mellitus; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; EuroSCORE, European system for cardiac operative risk evaluation.

regardless of associated left ventricular systolic dysfunction and appeared to vary with the severity of diastolic dysfunction, reaching statistical significance in grade III diastolic dysfunction. Patients with diastolic dysfunction also were more likely to experience major adverse cardiac events and prolonged mechanical ventilation. No difference was noted in the incidence of postoperative MI and AF between the 2 groups.

It has been known from very early studies that greater end-diastolic pressures among patients undergoing CABG were associated with greater preoperative mortality.²⁵ Among patients receiving surgery for coronary artery disease (CAD) or aortic stenosis, the incidence of left

ventricular diastolic dysfunction ranges between 44% and 75%.²⁶⁻²⁸ In our study, the difference between mortality in groups with delayed relaxation (stage I diastolic dysfunction) and pseudonormal pattern (stage II diastolic dysfunction) was not statistically significant compared with patients with normal diastolic function, despite relatively greater prevalence.^{17,20,23}

One possible explanation could be that with revascularization the milder forms of diastolic dysfunction improve, resulting in no difference in outcomes compared with those with normal diastolic function. Vaskelyte and colleagues²⁹ showed that LV wall motion score did not improve in 67% of patients with restrictive filling compared with

TABLE 3. NOS risk of bias scale for included cohort studies

Studies	Selection				Outcome of interest not present at start of study	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Comparability		Assessment of outcome	Adequacy of duration of follow-up	Adequacy of completeness of follow-up	
Afilalo, 2013	*	*	*	*	*(RV systolic dysfunction)	*	*	*	8
Bagheri, 2010	*	*	*	*		*	*	*	7
Bernard, 2001	*	*	*	*	** (age, CPB)	*	*	*	9
Değirmencioglu, 2013	*	*	*	*		*	*	*	7
Lee, 2012	*	*	*	*	*(LVEF)	*	*	*	8
Liu, 2003	*	*	*	*	** (age, LVEF)	*	*	*	9
Matyal, 2009	*	*	*	*	** (age, LVEF)	*	*	*	9
Melduni, 2011	*	*	*	*	** (age, hypertension)	*	*	*	9
Merello, 2008	*	*	*	*	** (age, renal failure)	*	*	*	9
Salem, 2006	*	*	*	*	** (age, LVEF)	*	*	*	9
Sastry, 2010	*	*	*	*	** (EuroSCORE)	*	*	*	9
Youn, 2011	*	*	*	*	** (EuroSCORE)	*	*	*	9

Each asterisk represents a score of 1 point. NOS scores >7 were considered high-quality studies, and NOS scores of 5-7 were considered moderate-quality studies. NOS, Newcastle Ottawa Scale; RV, right ventricle; CPB, cardiopulmonary bypass time; LVEF, left ventricular ejection fraction; EuroSCORE, European system for cardiac operative risk evaluation.

42% or 43% of patients with stage I or II diastolic dysfunction respectively, in the early postoperative period. Despite similar degrees of systolic dysfunction (LVEF <35%) and severity of CAD (93% patients had previous MI and 3-vessel disease), patterns of LV diastolic filling varied, perhaps based on the duration of CAD, and for the most part determined postoperative mortality. Myocyte relaxation during diastole is an energy-dependent process and thus sensitive to impaired perfusion.³⁰ Oppizzi and colleagues³¹ reported that diastolic dysfunction persisted during stay in the intensive care unit, and 3 months

after CABG it normalized in 85% of patients, and earlier studies have reported improvements beginning as early as 1 week.³² These studies are limited by less-than-optimal measurement tools for diastolic dysfunction. For these reasons, some have questioned the utility of cardiac surgery in patients with severe diastolic dysfunction, therefore making preoperative evaluation imperative in these patients.

Mortality and other adverse outcomes associated with diastolic dysfunction are not predicted adequately and actually exceeded that predicted by traditional risk scoring

FIGURE 2. Mortality after cardiovascular surgery in patients with and without diastolic dysfunction. CI, Confidence interval; M-H, Mantel-Haenszel.

Grade I vs normal

Grade II vs normal

Grade III vs normal

FIGURE 3. Postoperative mortality after cardiovascular surgery and grade of diastolic dysfunction: A, grade I versus normal; B, grade II versus normal; C, grade III versus normal. DD, Diastolic dysfunction; M-H, Mantel-Haenszel; CI, confidence interval.

systems such as EuroSCORE and Parsonnet in the pseudo-normal relaxation and restrictive filling subgroups.^{23,33} These risk scores vastly underestimate the mortality associated with diastolic dysfunction but, as expected, are good at predicting mortality associated with other extracardiac conditions. One reason is that there is scarce evidence of diastolic dysfunction as an independent predictor of adverse outcomes, especially mortality. Sastry and colleagues¹⁴ showed that further risk stratification of mortality by EuroSCORE is augmented by additional use of left ventricular end-diastolic pressure,

especially greater than 20 mm Hg and the leftward shift of the curve approaches actual mortality (area under ROC increased from 0.70 to 0.78).

Our study has several limitations. The impact of diastolic dysfunction on mortality, MACE, and other outcomes is unadjusted for other factors that influence diastolic function, particularly in the perioperative period. Most studies, however, excluded patients with confounders for ventricular preload, namely atrial arrhythmias, moderate-to-severe valvular dysfunction, and chronic renal failure (Table 1) but this amounts up to at

FIGURE 4. Complications after cardiovascular surgery in patients with diastolic dysfunction: A, MACE; B, myocardial infarction; C, atrial fibrillation; D, prolonged mechanical ventilation. *MACE*, Major adverse cardiovascular events; *IV*, inverse variance; *CI*, confidence interval.

least 20% of patients undergoing cardiac surgery in whom diastolic dysfunction cannot be accurately measured.³⁴ Adjusted risk estimates wherever available are provided in Table E1. As far the confounding from diastolic dysfunction associated with possible ischemic heart disease, our subgroup analysis found no impact of LV systolic dysfunction on the relationship between diastolic dysfunction and mortality. Individual studies also have shown that LVEF and left main disease did not provide independent prognostic value over LV end-diastolic diameter

and deceleration time in predicting mortality.^{23,24} We were limited in the use of studies that provided E/e as the measure of diastolic dysfunction³⁵ that is known to limit confounding from moderate-to-severe aortic stenosis and secondary mitral regurgitation.^{36,37} Also, different measures of diastolic dysfunction were used among studies; however, grading of diastolic dysfunction was reported consistently across studies. As far the impact of diastolic dysfunction on vascular surgery, we could only find one study. Scarcity of outcomes and studies

complicated the analyses; however, we used the Mantel-Haenszel fixed-effects model to provide the best effect estimates in this situation and sensitivity analyses with the arcsine method (random effects model) provided similar results. The use of random effects models usually is the best choice when authors believe that there is substantial methodologic heterogeneity (differences in populations, sample sizes, interventions, controls, follow up times, outcomes) or statistical heterogeneity (differences in effects) across studies; however, the use of fixed effects is the primary choice when the number of outcomes is scarce (ie, <10% of the group total) or when there is imbalance of groups (different sample sizes) in most of the studies. In these cases, the fixed effects models give a more robust effect metric in comparison to the random effects model. As sensitivity analysis random effects model should also be used to evaluate the consistency or not of the effects between the two models. Additionally, this work is meant to be hypothesis generating and would need to be confirmed in future prospective studies.

In summary, the true and independent impact of diastolic dysfunction of postoperative cardiovascular outcomes is difficult to assess. The current risk scoring systems do not include diastolic dysfunction for risk stratification and may need to be re-evaluated.

Conflict of Interest Statement

Dr Deepak L. Bhatt discloses the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Vice-Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix,

Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical; Trustee: American College of Cardiology; Unfunded Research: FlowCo, PLx Pharma, Takeda. Dr Bueno reports having received consulting/speaking fees from Abbott, Astra-Zeneca, Bayer, BMS-Pfizer, Daichii-Sankyo, Eli-Lilly, Ferrer, Menarini, Novartis, Sanofi, Servier, and a research grant from Astra-Zeneca. All other authors have nothing to disclose with regard to commercial support.

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