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Grade 3 Echocardiographic Diastolic Dysfunction Is Associated With Increased Risk of Major Adverse Cardiovascular Events After Surgery: A Retrospective Cohort Study

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BACKGROUND: Diastolic dysfunction is common and may increase the risk of cardiovascular complications. This study investigated the hypothesis that, in patients with isolated left ventricular diastolic dysfunction, higher grade diastolic dysfunction was associated with greater risk of major adverse cardiovascular events (MACEs) after surgery.

METHODS: This was a retrospective cohort study. Data of adult patients with isolated echocardiographic diastolic dysfunction (ejection fraction, ≥50%) who underwent noncardiac surgery from January 1, 2015 to December 31, 2015 were collected. The primary end point was the occurrence of postoperative MACEs during hospital stay, which included acute myocardial infarction, congestive heart failure, stroke, nonfatal cardiac arrest, and cardiac death. The association between the grade of diastolic dysfunction and the occurrence of MACEs was assessed with a multivariable logistic model.

RESULTS: A total of 2976 patients were included in the final analysis. Of these, 297 (10.0%) developed MACEs after surgery. After correction for confounding factors, grade 3 diastolic dysfunction was associated with higher risk of postoperative MACEs (odds ratio, 1.71; 95% confidence interval, 1.28–2.27; $P < .001$) when compared with grades 1 and 2. Patients with grade 3 diastolic dysfunction developed more non-MACE complications when compared with grades 1 and 2 (uncorrected odds ratio, 1.44; 95% confidence interval, 1.07–1.95; $P = .017$).

CONCLUSIONS: In patients with isolated diastolic dysfunction undergoing noncardiac surgery, 10.0% develop MACEs during hospital stay after surgery; grade 3 diastolic dysfunction is associated with greater risk of MACEs. (Anesth Analg 2019;129:651–8)

KEY POINTS

- **Question:** Does the severity of echocardiographic left ventricular diastolic dysfunction affect postoperative outcomes?
- **Findings:** Grade 3 diastolic dysfunction, relative to grades 1 and 2 severity, was associated with a higher risk of major adverse cardiovascular events after noncardiac surgery.
- **Meaning:** Care should be taken when managing patients with grade 3 diastolic dysfunction during the perioperative period, although more studies are required.

Diastolic dysfunction refers to impaired left ventricular (LV) relaxation with or without an increase of filling pressure.[1] It can be present in asymptomatic patients, patients with preserved ejection fraction (EF), and patients with reduced EF.[2] Diastolic dysfunction as detected by comprehensive Doppler techniques is common. For example, in a study of a community population ≥45 years of age, 20.8% had mild, 6.6% had moderate, and 0.7% had severe diastolic dysfunction, with 5.6% of the population having moderate-to-severe diastolic dysfunction with normal EF.[3] The prevalence of diastolic dysfunction varies among different populations; it is 2.8% in individuals 25–30 years of age and 15.8% in those >65 years of age, and the prevalence is higher in men than in women (13.8% vs 8.6%).[4] Although diastolic dysfunction

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Brief summary statement: Patients (10.0%) with isolated diastolic dysfunction developed major adverse cardiovascular events after noncardiac surgery. When compared with diastolic dysfunction of grades 1 and 2, grade 3 was independently associated with greater risk of major adverse cardiovascular events.

Trial Registration: ClinicalTrials (clinicaltrials.gov) NCT03138109.

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is often symptomless, its presence is associated with marked increases of all-cause mortality.[3]

According to available evidence, age, hypertension, diabetes, and LV hypertrophy are major risk factors of diastolic dysfunction.[5] Along with the aging population, it can be expected that more and more patients with diastolic dysfunction will be encountered in the operating room and will constitute a big challenge for perioperative care. Indeed, in a recent meta-analysis, the presence of diastolic dysfunction is significantly associated with an increased risk of major adverse cardiovascular events (MACEs) in surgical patients.[6] However, in that meta-analysis, reviewers' overall certainty of the evidence was moderate.[6] Therefore, further evidence is needed to evaluate the impact of diastolic dysfunction on postoperative outcomes.

This study was aimed to investigate the hypothesis that, in patients with isolated echocardiographic diastolic LV dysfunction, higher grade diastolic dysfunction was associated with greater risk of MACEs after noncardiac surgery.

METHODS

Study Design

This retrospective cohort study was approved by the Peking University First Hospital Ethics Committee (2015 [965]). Because of the retrospective nature and that no patient follow-up was performed, the requirement for written informed consent was waived by the ethics committee. The trial was registered at clinicaltrials.gov (NCT03138109; principal investigator: Y.Z.; date of registration: May 3, 2017).

Patient Collection

Patients who had preoperative results of echocardiographic examination were screened for study inclusion. As a routine practice in the study center, those who were ≥60 years of age or had history of cardiovascular disease were required to undergo echocardiographic examination before surgery. The inclusion criteria were adult (≥18 years of age) patients who were diagnosed as diastolic LV dysfunction by echocardiography within 90 days before surgery and underwent noncardiac surgery in Peking University First Hospital from January 1, 2015 to December 31, 2015. The exclusion criteria include congenital heart disease, moderate-to-severe valvular disease (stenosis or insufficiency), atrial fibrillation or other tachyarrhythmia, pericarditis, unsatisfied echocardiogram, LV EF <50%, American Society of Anesthesiologists (ASA) classification of V or higher, or missed or incomplete preoperative echocardiographic results.

Transthoracic Echocardiography

All enrolled patients received echocardiographic examination within 90 days before surgery. Two types of ultrasound machines (Philips IE33 [Philips Medical Systems, Andover, MA] and GE Vivid E9 [GE Vingmed Ultrasound AS, Horten, Norway]) were used, with the probe frequency of 2–4 MHz and frame rate of >50 frames/s. Patients were examined at rest in the left lateral position. Standard 2-dimensional and Doppler images were collected by cardiologists. Images were interpreted by cardiologists with ≥5 years of working experience.

Data collection included left atrial diameter, peak E (early diastolic) and A (late diastolic) velocities, deceleration time (DT) from E peak, pulsed-wave tissue Doppler image E′ velocity (in centimeters per second), mitral E/A ratio, and mitral E/e′ ratio. The e′ wave was measured on the septal side of the mitral valve. Diastolic dysfunction was diagnosed according to the echocardiographic examination results and categorized into 3 grades based on 2009 version of recommendations, that is, grade 1 (mild diastolic dysfunction or impaired relaxation phase: E/A <0.8, DT >200 milliseconds, E/e′ ≤8), grade 2 (moderate diastolic dysfunction or pseudonormal phase: E/A 0.8–1.5, DT 160–200 milliseconds, E/e′ 9–12), and grade 3 (severe diastolic dysfunction or restrictive filling phase: E/A ≥2, DT <160 milliseconds, E/e′ ≥13).[1] Cardiologists (L.L. and B.-W.Z.) were consulted when there was difficulty in categorizing the grades according to the criteria listed above.

Baseline and Intraoperative Data Collection

Patients were screened in the electronic record system of the Department of Cardiology according to the inclusion and exclusion criteria. For enrolled patients, detailed data collection was performed in the electronic record system of the hospital. Preoperative data included demographic data (age, body mass index, and sex), comorbidity, medication, results of echocardiographic examination (including grade of diastolic dysfunction), and ASA physical status classification. Intraoperative data included diagnosis, anesthetic information (type, duration, fluid infusion, use of vasoactive drugs, and urine output), surgical information (type, duration, and blood loss), and the complexity of the surgical procedure (divided into low, moderate, or high risk according to the modified Johns Hopkins surgical criteria).[7]

Postoperative Outcomes

The primary end point was the occurrence of MACEs during hospitalization after surgery, including acute myocardial infarction, congestive heart failure, stroke, nonfatal cardiac arrest, and cardiac death.[8,9] Diagnosis of acute myocardial infarction required clinical symptoms and/or new electrocardiographic abnormalities and a cardiac troponin I of >0.05 ng/mL; congestive heart failure required signs and symptoms of heart failure and a B-type natriuretic peptide ≥400 pg/mL; stroke required new-onset localized neurological symptoms or unconsciousness, confirmed by computed tomography or magnetic resonance imaging scanning; nonfatal cardiac arrest required the occurrence of sudden cardiac arrest but successful resuscitation, that is, spontaneous circulation returned and patient survived; and cardiac death required sufficient evidence to prove that death occurred due to cardiac causes.[10–13]

Secondary end points included admission to intensive care unit after surgery, incidence of non-MACE complications during hospitalization, length of stay in hospital after surgery, and in-hospital mortality. Non-MACE complications were generally defined as new-onset medical conditions other than MACEs that were unfavorable to patient recovery and required therapeutic intervention during hospitalization after surgery. The diagnostic criteria for each individual non-MACE complication are listed in Supplemental Digital Content, Table 1, http://links.lww.com/AA/C584.

Postoperative outcomes were assessed by 2 investigators (Y.Z. and T.C.) who reviewed the electronic medical documents of all enrolled patients; these included the medical histories; results of physical, laboratory, and auxiliary examinations; medical consultation records; and records of death discussion. The occurrence of MACEs and non-MACE complications was diagnosed according to the predefined definitions and was cross-checked by the 2 investigators. Cardiologists (L.L. and B.-W.Z.) and/or a senior anesthesiologist (D.-X.W.) were consulted when there were discrepancies regarding diagnosis.

Statistical Analysis

According to previous studies,[14–17] we assumed that the incidence of postoperative MACEs would be 7.1% and 18.0% in patients with grade 2 and grade 3 diastolic dysfunction, respectively. With significance set at 0.05/3 = 0.0167 and power set at 90%, the calculated sample size needed to compare 3 proportions was 296 patients in each group. For comparison among 3 groups, we needed ≥888 patients.[18]

For comparative analysis, patients were divided into 3 groups according to their grades of diastolic dysfunction. Continuous variables with normal distribution were compared with 1-way analysis of variance; those with nonnormal distribution were compared with the Kruskal–Wallis *H* test. The Kolmogorov–Smirnov test was used for testing normality. Categorical variables were compared with the χ^2 test or continuity correction χ^2 test. Rank variables were compared with the Kruskal–Wallis *H* test.

Factors that were possibly associated with the development of MACEs were screened with univariable logistic regression analyses and tested for collinearity. Because the number of patients with grade 1 diastolic dysfunction was relatively small and there was no significant difference between grades 1 and 2 diastolic dysfunction regarding their association with postoperative MACE development, patients with grades 1 and 2 diastolic dysfunction were combined for further analyses. Those who had *P* values <.10 in univariable analysis were included in a multivariable logistic regression model to identify an association between the severity of diastolic dysfunction and the development of MACEs.

A two-tailed test was performed whenever appropriate, and *P* values of <.05 were considered statistically significant. For multiple comparisons among 3 grades of diastolic dysfunction, the criterion of significance was adjusted with Bonferroni correction ($P < .05/3 = .0167$). Statistical analyses were performed with SPSS 17.0 software (SPSS, Chicago, IL) and R (3.2.3), Statistics Department of the University of Auckland, Auckland, New Zealand.

RESULTS

Patient Population

From January 1, 2015 to December 31, 2015, 4347 patients who underwent echocardiographic examination within 90 days before surgery were screened. Of these, 2976 met the inclusion/exclusion criteria and were included in the final analysis (Figure). Among included patients, 262 (8.8%) were diagnosed as diastolic dysfunction grade 1, 1611 (54.1%) grade 2, and 1103 (37.1%) grade 3. The baseline and intraoperative data are listed in Tables 1–2 and Supplemental Digital Content, Table 2, http://links.lww.com/AA/C584.

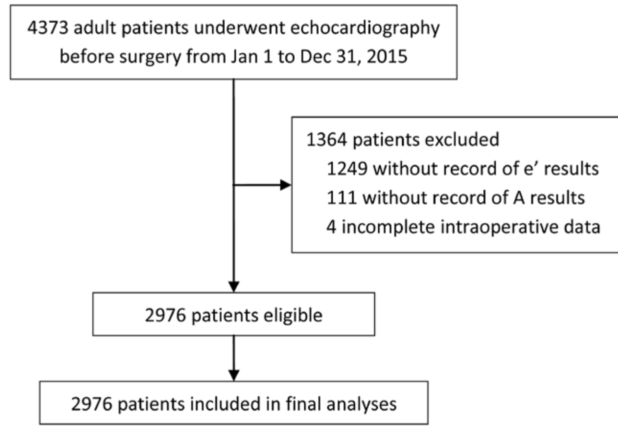

Figure. Flowchart of the study. A indicates late diastolic mitral velocity; e′, peak early diastolic mitral annulus velocity.

Occurrence of Postoperative MACEs and Non-MACE Complications

Among the included 2976 patients, 297 (10.0%) developed ≥1 MACE during hospital stay after surgery. For those who developed MACEs, 247 (8.3%) were congestive heart failure, 110 (3.7%) acute myocardial infarction (including 5 ST-elevation myocardial infarction and 105 non–ST-elevation myocardial infarction), 13 (0.4%) stroke, and 4 (0.1%) cardiovascular death (Table 3). The MACEs (80.1% [238 of 297]) occurred within 3 days after surgery (Supplemental Digital Content, Figure 1, http://links.lww.com/AA/C584). Post hoc multiple comparisons showed a higher incidence of postoperative MACEs in patients with grade 3 diastolic dysfunction (grade 2 vs grade 1: 7.3% [118/1611] vs 7.3% [19/262], *P* = .971; grade 3 vs grade 1: 14.5% [160/1103] vs 7.3% [19/262], *P* = .001; grade 3 vs grade 2: 14.5% [160/1103] vs 7.3% [118/1611], *P* < .001). When compared to patients with grades 1 and 2 diastolic dysfunction, those with grade 3 diastolic dysfunction developed more MACEs (uncorrected odds ratio [OR], 2.05; 95% confidence interval [CI], 1.61–2.62; *P* < .001); they also developed more non-MACE complications (uncorrected OR, 1.44; 95% CI, 1.07–1.95; *P* = .017) (Table 3; Supplemental Digital Content, Table 3, http://links.lww.com/AA/C584).

Factors in Association With Development of Postoperative MACEs

After testing for collinearity, 24 factors that were identified by univariate analyses (*P* < .10) were included in a multivariable model. Multivariable logistic regression analysis (backward stepwise method) identified 16 factors that were significantly associated with the development of postoperative MACEs. Of these, grade 3 diastolic dysfunction was associated with an increased risk of postoperative MACEs when compared with grades 1 and 2 (OR, 1.71; 95% CI, 1.28–2.27; *P* < .001). Among 15 other factors, age ≥70 years (compared with <50 years), body mass index <18.5 kg/m^2 (compared with 18.5–24.9 kg/m^2), hypertension, coronary heart disease, arrhythmia, renal insufficiency, regular glucocorticoid therapy, symptomatic diastolic dysfunction, ASA classification grades III and IV (compared with grades I and II), intraoperative use of vasopressors or antihypertensives, intraoperative fluid infusion rate ≥9.0 mL/kg/h (compared

Table 1. Baseline Data

		Grade of Diastolic Dysfunction[a]			
Items	**All (n = 2976)**	**Grade 1 (n = 262)**	**Grade 2 (n = 1611)**	**Grade 3 (n = 1103)**	***P* Value**
Age (y)	65.3 ± 13.0	65.0 ± 13.3	65.0 ± 13.2	65.8 ± 12.7	.240
Male	1341 (45.1)	112 (42.7)	727 (45.1)	502 (45.5)	.713
Body mass index (kg/m^2)	24.6 ± 4.6	24.5 ± 3.8	24.5 ± 3.8	24.6 ± 3.9	.635
Preoperative comorbidity					
Hypertension	1442 (48.5)	119 (45.4)	772 (47.9)	551 (50.0)	.332
Diabetes	569 (19.1)	42 (16.0)	300 (18.6)	227 (20.6)	.180
Diabetes on insulin	180 (6)	12 (4.6)	91 (5.6)	77 (7.0)	.207
Coronary heart disease	424 (14.2)	21 (8.0)	229 (14.2)	174 (15.8)	.005[b]
Previous stroke	312 (10.5)	24 (9.2)	168 (10.4)	120 (10.9)	.709
Dyslipidemia	255 (8.6)	18 (6.9)	128 (7.9)	109 (9.9)	.121
Renal insufficiency[c]	160 (5.4)	21 (8.0)	84 (5.2)	55 (5.0)	.136
Arrhythmia	140 (4.7)	11 (4.2)	76 (4.7)	53 (4.8)	.915
Peripheral vascular disease	91 (3.1)	3 (1.1)	52 (3.2)	36 (3.3)	.169
COPD	94 (3.2)	8 (3.1)	49 (3.0)	37 (3.4)	.894
Liver diseases[d]	70 (2.4)	9 (3.4)	36 (2.2)	25 (2.3)	.480
Regular glucocorticoid therapy[e]	26 (0.9)	2 (0.8)	10 (0.6)	14 (1.3)	.199
ASA classification					.725[f]
I	262 (8.8)	31 (11.8)	145 (9.0)	86 (7.8)	
II	2319 (77.9)	200 (76.3)	1253 (77.8)	866 (78.5)	
III	387 (13)	30 (11.5)	210 (13.0)	147 (13.3)	
IV	8 (0.3)	1 (0.4)	3 (0.2)	4 (0.4)	
LVEF (%)	70.5 ± 6.5	70.7 ± 5.8	70.5 ± 6.3	70.6 ± 6.9	.834
Symptomatic diastolic dysfunction[g]	33 (1.1)	2 (0.8)	12 (0.7)	19 (1.7)	.049[h]

Data are presented as mean ± standard deviation or number (%).

Abbreviations: ASA, American Society of Anesthesiologists; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction.

[a]According to the 2009 recommendations for the evaluation of LV diastolic function by echocardiography.[1]

[b]Grade 2 versus grade 1, $P = .006$; grade 3 versus grade 1, $P = .005$; grade 3 versus grade 2, $P = .254$ (χ^2 tests). $P < .0167$ was considered statistically significant (Bonferroni correction); same for the following post hoc multiple comparisons.

[c]Preoperative creatinine ≥133 mmol/L.

[d]Include virus hepatitis, cirrhosis, and/or enzyme abnormality (≥2 times upper limits).

[e]With a duration of >1 mo.

[f]Analyzed as ordered factors with Kruskal–Wallis *H* test.

[g]Defined as the presence of symptoms (shortness of breathing) and signs (chest x-ray findings) suggesting heart failure, a serum BNP >400 pg/mL, and/or a typical clinical response to diuretic therapy in patients with echocardiographic diastolic dysfunction and normal EF (≥50%). For all these patients, diagnosis was confirmed by consulting cardiologists and treatment were initialized before surgery.

[h]Grade 2 versus grade 1, $P = .974$; grade 3 versus grade 1, $P = .257$; grade 3 versus grade 2, $P = .019$ (χ^2 tests).

with <5.0 mL/kg/h), cancer surgery, duration of surgery ≥120 minutes (compared with <120 minutes), and medium- and high-grade complexity of surgery (compared with low-grade complexity) were associated with increased risk of MACEs, whereas body mass index ≥30 kg/m^2 (compared with 18.5–24.9 kg/m^2) was associated with a decreased risk of MACEs (Table 4).

DISCUSSION

Our results showed that, in patients with isolated echocardiographic diastolic dysfunction, 10.0% developed MACEs after noncardiac surgery. Higher-grade (grade 3) diastolic dysfunction was associated with a greater risk of postoperative MACEs.

The reported incidences of MACEs vary in different patient populations. For example, in patients with isolated diastolic LV dysfunction undergoing vascular surgery, the incidence of postoperative adverse cardiovascular events ranged from 18% to 38%.[14,15] In patients with diastolic dysfunction who underwent liver transplantation, the incidence of cardiovascular complications was 4% and the rate of mortality was 14% early after surgery.[16] In a study of patients undergoing noncardiac surgery by Cho et al,[17] the incidence of postoperative MACEs was 7.1% in all patients, but it was higher (about 8%) in those with an E/e′ ratio >15 (indicating the presence of diastolic dysfunction) than in those with an E/e′ ratio ≤15. The present study was performed in patients with isolated echocardiographic diastolic dysfunction who underwent noncardiac surgery. Postoperative MACEs developed in 10.0% of our patients, within the range of the previously reported incidences.

The impacts of diastolic LV dysfunction on postoperative outcomes remain controversial. Some studies reported that the existence of diastolic dysfunction did not influence postoperative outcomes,[16,19,20] whereas some others found that preoperative diastolic dysfunction was associated with increased complications and even mortality after surgery.[14,21,22] Reasons leading to conflicting results may include differences in sample size, target patients, and perioperative care management. A recent meta-analysis concluded that perioperative diastolic dysfunction is an independent risk factor for adverse cardiovascular outcomes after noncardiac surgery with, however, moderate certainty of evidence.[6] Furthermore, in the above studies, the definitions of diastolic dysfunction were different, and the impacts of diastolic dysfunction severity on the outcomes were not clear. In the present study, all included patients had isolated echocardiographic diastolic dysfunction, of which the severity was diagnosed according to the guidelines.[1] Our results

Table 2. Intraoperative Data

Items	All (n = 2976)	Grade of Diastolic Dysfunction[a] Grade 1 (n = 262)	Grade 2 (n = 1611)	Grade 3 (n = 1103)	*P* Value
Duration of anesthesia (min)	241 ± 136	245 ± 139	240 ± 135	242 ± 137	.811
Type of anesthesia					.477
Regional[b]	486 (16.3)	48 (18.3)	253 (15.7)	185 (16.8)	
General	2328 (78.2)	195 (74.4)	1273 (79.0)	860 (77.9)	
Combined	162 (5.4)	19 (7.3)	85 (5.3)	58 (5.3)	
Fluid infusion (mL)	1600 (1100–2350)	1600 (1100–2488)	1600 (1100–2400)	1600 (1100–2238)	.585
Fluid infusion rate (mL/kg/h)					.546[c]
<5.0	454 (15.3)	38 (14.5)	245 (15.2)	171 (15.5)	
5.0–6.9	844 (28.4)	77 (29.4)	463 (28.7)	304 (27.6)	
7.0–8.9	739 (24.8)	72 (27.5)	387 (24.0)	280 (25.4)	
≥9.0	939 (31.6)	75 (28.6)	516 (32.0)	348 (31.6)	
Blood transfusion (%)	423 (14.2)	46 (17.6)	221 (13.7)	156 (14.1)	.256
Estimated blood loss (mL)	50 (0–200)	50 (0–245)	50 (0–200)	50 (0–200)	.619
Urine output (mL)	300 (50–600)	300 (62–700)	300 (50–600)	300 (50–600)	.674
Use of vasopressors[d]	317 (10.7)	34 (13.0)	158 (9.8)	125 (11.3)	.197
Use of antihypertensives[e]	438 (14.7)	42 (16.0)	233 (14.5)	163 (14.8)	.800
Cancer surgery	1351 (45.4)	127 (48.5)	721 (44.8)	502 (45.5)	.528
Duration of surgery (min)	164 ± 118	169 ± 122	163 ± 117	164 ± 119	.749
Complexity of surgery[f]					.648
Low	420 (14.1)	30 (11.5)	227 (14.1)	163 (14.8)	
Medium	1642 (55.2)	144 (55.0)	892 (55.4)	606 (54.9)	
High	914 (30.7)	88 (33.6)	492 (30.5)	334 (30.3)	

Data are presented as mean ± standard deviation, number (%), or median (interquartile range).
Abbreviation: LV, left ventricular.
[a]According to the 2009 recommendations for the evaluation of LV diastolic function by echocardiography.[1]
[b]Included neuraxial block, peripheral nerve block, and local infiltration.
[c]Analyzed as ordered factors with Kruskal–Wallis *H* test.
[d]Included adrenaline and/or dopamine.
[e]Included urapidil and/or nicardipine.
[f]According to modified Johns Hopkins surgical criteria.[8]

Table 3. Postoperative Outcomes

Items	All (n = 2976)	Grade of Diastolic Dysfunction[a] Grade 1 (n = 262)	Grade 2 (n = 1611)	Grade 3 (n = 1103)	*P* Value
MACEs	297 (10.0)	19 (7.3)	118 (7.3)	160 (14.5)	<.001[b]
Congestive heart failure	247 (8.3)	11 (4.2)	103 (6.4)	133 (12.1)	<.001[c]
Acute myocardial infarction[d]	110 (3.7)	9 (3.4)	41 (2.5)	60 (5.4)	<.001[e]
Stroke	13 (0.4)	3 (1.1)	5 (0.3)	5 (0.5)	.164
Cardiovascular death	4 (0.1)	0 (0.0)	2 (0.1)	2 (0.2)	.761
Non-MACE complications	183 (6.1)	14 (5.3)	85 (5.3)	84 (7.6)	.038[f]
ICU admission	322 (10.8)	28 (10.7)	157 (9.7)	137 (12.4)	.086
Length of ICU stay (d)[g,h]	1 (1–2), 2.8 ± 4.8	1 (1–3.8), 3.6 ± 7.5	1 (1–2), 2.8 ± 5.4	1 (1–3), 2.6 ± 3.0	.219
Mechanical ventilation (h)[g,h]	2 (0–7), 12.3 ± 59.6	0 (0–7), 5.5 ± 13.7	3 (0–8), 12.3 ± 69.5	2 (0–7), 13.6 ± 52.7	.717
Length of hospital stay (d)[h]	7 (4–11), 9.1 ± 9.3	7 (4–10), 8.5 ± 7.4	7 (4–10), 8.6 ± 9.1	7 (4–12), 9.9 ± 9.9	.059
In-hospital day mortality	8 (0.3)	0 (0.0)	5 (0.3)	3 (0.3)	.667

Data are presented as number (%) or median (IQR) and mean ± standard deviation.
Abbreviations: ICU, intensive care unit; IQR, interquartile range; LV, left ventricular; MACE, major adverse cardiac events.
[a]According to the 2009 recommendations for the evaluation of LV diastolic function by echocardiography.[1]
[b]Grade 2 versus grade 1, $P = .971$; grade 3 versus grade 1, $P = .001$, grade 3 versus grade 2, $P < .001$ (χ^2 tests). $P < .0167$ was considered statistically significant (Bonferroni correction); same for the following post hoc multiple comparisons.
[c]Grade 2 versus grade 1, $P = .697$; grade 3 versus grade 1, $P < .001$; grade 3 versus grade 2, $P < .001$ (χ^2 tests).
[d]Include 5 cases of ST-elevation myocardial infarction and 105 cases of non–ST-elevation myocardial infarction.
[e]Grade 2 versus grade 1, $P = .479$; grade 3 versus grade 1, $P = .367$; grade 3 versus grade 2, $P < .001$ (χ^2 tests).
[f]Grade 2 versus grade 1, $P > .999$; grade 3 versus grade 1, $P = .232$; grade 3 versus grade 2, $P = .015$ (χ^2 tests).
[g]Results of patients who were admitted to the ICU.
[h]Analyzed with Kruskal–Wallis *H* tests. Results are presented as median (IQR) and mean ± standard deviation.

showed that, after correction for confounding factors, high-grade (grade 3) diastolic dysfunction was associated with a higher risk of postoperative MACEs; the presence of symptomatic diastolic dysfunction before surgery was also associated with a higher risk of postoperative MACEs. Therefore, considering our results together with others, care should be taken when managing patients with high-grade diastolic dysfunction, especially those with clinical symptoms, during the perioperative period, although further studies are needed to clarify this problem.

In our results, low body mass index (<18.5 kg/m^2) was correlated with increased risk, whereas high body mass index (>30 kg/m^2) was correlated with reduced risk of postoperative MACEs. Romero-Corral et al[23] also reported

Table 4. Factors in Association With the Development of Postoperative MACEs

	Univariable		Multivariable[a]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (y)				
<50	Reference		Reference	
50–59	0.90 (0.45–1.79)	.769	0.95 (0.44–2.06)	.902
60–69	1.87 (1.05–3.32)	.034	1.87 (0.95–3.66)	.069
≥70	3.36 (1.91–5.89)	<.001	3.82 (1.97–7.39)	<.001
Male gender	2.04 (1.60–2.61)	<.001	…	…
Body mass index (kg/m^2)				
18.5–24.9	Reference		Reference	
<18.5	2.26 (1.45–3.51)	<.001	1.80 (1.03–3.16)	.039
25.0–29.9	0.76 (0.58–0.99)	.039	0.80 (0.59–1.10)	.177
≥30.0	0.25 (0.12–0.54)	<.001	0.37 (0.16–0.84)	.017
Preoperative comorbidity				
Hypertension	1.57 (1.23–2.00)	<.001	1.36 (1.01–1.83)	.045
Diabetes on insulin	2.15 (1.45–3.21)	<.001	…	…
Coronary heart disease	2.35 (1.77–3.12)	<.001	1.88 (1.31–2.69)	.001
Previous stroke	1.76 (1.26–2.46)	.001	…	…
Dyslipidemia	1.85 (1.29–2.64)	.001	…	…
Renal insufficiency[b]	2.51 (1.68–3.76)	<.001	1.90 (1.13–3.19)	.015
Arrhythmia	2.50 (1.63–3.84)	<.001	1.98 (1.19–3.29)	.009
COPD	2.05 (1.20–3.52)	.009	…	…
Regular glucocorticoid therapy[c]	3.38 (1.41–8.10)	.006	4.05 (1.49–11.00)	.006
ASA classification				
Grades I and II	Reference		Reference	
Grades III and IV	3.65 (2.78–4.79)	<.001	1.99 (1.41–2.8)	<.001
LVEF (%)				
50–59	Reference		…	…
60–69	0.57 (0.35–0.95)	.032	…	…
≥70	0.44 (0.27–0.72)	.001	…	…
Diastolic dysfunction[d]				
Grades 1 and 2	Reference		Reference	
Grade 3	2.05 (1.61–2.62)	<.001	1.71 (1.28–2.27)	<.001
Symptomatic diastolic dysfunction[e]	30.69 (13.71–68.70)	<.001	21.89 (8.44–56.73)	<.001
Type of anesthesia				
Regional[f]	Reference		…	…
General and combined	0.36 (0.23–0.57)	<.001	…	…
Fluid infusion rate (mL/kg/h)				
<5.0	Reference		Reference	
5.0–6.9	0.98 (0.64–1.51)	.935	0.88 (0.54–1.42)	.588
7.0–8.9	1.37 (0.90–2.09)	.138	1.27 (0.79–2.05)	.33
≥9.0	1.79 (1.21–2.65)	.004	1.74 (1.08–2.78)	.022
Blood infusion	2.26 (1.70–3.01)	<.001	…	…
Use of vasopressors[g]	3.11 (2.31–4.18)	<.001	1.49 (1.03–2.13)	.033
Use of antihypertensives[h]	2.34 (1.77–3.10)	<.001	1.55 (1.12–2.14)	.008
Cancer surgery	2.21 (1.73–2.83)	<.001	1.59 (1.17–2.15)	.003
Duration of surgery (min)				
<120	Reference		Reference	
120–239	2.86 (2.07–3.95)	<.001	2.30 (1.54–3.41)	<.001
240–479	4.36 (3.12–6.10)	<.001	3.86 (2.48–6.03)	<.001
≥480	12.49 (6.88–22.7)	<.001	13.65 (6.56–28.42)	<.001
Complexity of surgery[i]				
Low	Reference		Reference	
Medium	8.34 (3.67–18.95)	<.001	5.58 (2.29–13.62)	<.001
High	9.83 (4.29–22.54)	<.001	8.18 (3.22–20.81)	<.001

Abbreviations: ASA, American Society of Anesthesiologists; BNP, B-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; OR, odds ratio.

[a]Factors that had *P* values <.10 in univariable analysis were included in the multivariable logistic regression model. Logistic regression analysis was performed with backward stepwise method.

[b]Preoperative creatinine ≥133 mmol/L.

[c]With a duration of >1 mo.

[d]According to the 2009 left ventricular diastolic function assessment guidelines.[1]

[e]Defined as the presence of symptoms (shortness of breathing) and signs (chest x-ray findings), suggesting heart failure, a serum BNP >400 pg/mL, and/or a typical clinical response to diuretic therapy.

[f]Included neuraxial block, peripheral nerve block, and local infiltration.

[g]Included adrenaline and/or dopamine.

[h]Included urapidil and/or nicardipine.

[i]According to modified Johns Hopkins surgical criteria.[8]

that, in patients with coronary artery disease, those who were overweight (25–29.9 kg/m^2) had lower mortality. In line with previous studies,[14,24] preoperative hypertension, coronary heart disease, arrhythmia, and renal insufficiency were also associated with an increased risk of postoperative MACEs in our patients. Long-term glucocorticoid therapy increases the risk of cardiovascular disease.[25–27] This was also the case in surgical patients. In the present study, patients receiving vasoactive drugs (vasopressors and/or antihypertensives) were at an increased risk of MACEs. This phenomenon might be attributed to the hemodynamic fluctuations during surgery[9] but requires further investigation. As expected, rapid fluid infusion rate, prolonged duration of surgery, and complex surgery were associated with increased postoperative MACEs.

Our study had several limitations. First, because preoperative echocardiographic examination was mainly performed in the elderly or those with cardiovascular diseases, patients included in the study were actually "high-risk" ones. This limited the generalizability of our results. Second, we only included patients with diastolic LV dysfunction. And, due to the selection of "high-risk" patients, those with grade 1 diastolic dysfunction were less and were combined with grade 2 for analysis. These limited our insight into the impact of low-grade diastolic dysfunction on the outcomes. Third, limited by the method detecting diastolic dysfunction, patients with atrial fibrillation or other tachyarrhythmia, moderate-to-severe valvular disease, or pericarditis were not assessed for diastolic function. Results of our study cannot be extrapolated to these patients. Last, due to the retrospective design, residual confounding cannot be excluded. Despite these, our results provide clues for further investigation.

CONCLUSIONS

In patients with isolated echocardiographic diastolic dysfunction, 10% develop MACEs during hospital stay after noncardiac surgery; grade 3 diastolic dysfunction is independently associated with increased risk of postoperative MACEs. ■

DISCLOSURES

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Name: Lin Liu, MD.
Contribution: This author helped collect data on echocardiographic examination.
Name: Tong Cheng, MD.
Contribution: This author helped collect perioperative data.
Name: Dong-Xin Wang, MD, PhD.
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REFERENCES

1. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10:165–193.
2. LeWinter MM, Meyer M. Mechanisms of diastolic dysfunction in heart failure with a preserved ejection fraction: if it's not one thing it's another. *Am Heart Assoc*. 2013;6:1112–1115.
3. HEART C. Burden of systolic and diastolic ventricular dysfunction in the community. *JAMA*. 2003;289:194–202.
4. Fischer M, Baessler A, Hense HW, et al. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. *Eur Heart J*. 2003;24:320–328.
5. Jeong EM, Dudley SC Jr. Diastolic dysfunction. *Circ J*. 2015;79:470–477.
6. Fayad A, Ansari MT, Yang H, Ruddy T, Wells GA. Perioperative diastolic dysfunction in patients undergoing noncardiac surgery is an independent risk factor for cardiovascular events: a systematic review and meta-analysis. *Anesthesiology*. 2016;125:72–91.
7. Donati A, Ruzzi M, Adrario E, et al. A new and feasible model for predicting operative risk. *Br J Anaesth*. 2004;93:393–399.
8. Bae MH, Lee JH, Yang DH, Park HS, Cho Y, Chae SC. Usefulness of surgical parameters as predictors of postoperative cardiac events in patients undergoing non-cardiac surgery. *Circ J*. 2014;78:718–723.
9. Xu L, Yu C, Jiang J, et al. Major adverse cardiac events in elderly patients with coronary artery disease undergoing noncardiac surgery: a multicenter prospective study in China. *Arch Gerontol Geriatr*. 2015;61:503–509.
10. Amsterdam EA, Wenger NK, Brindis RG, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344–e426.
11. McMurray JJ, Adamopoulos S, Anker SD, et al; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2012;14:803–869.
12. Roffi M, Patrono C, Collet JP, et al; ESC Scientific Document Group. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.
13. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520.
14. Flu WJ, van Kuijk JP, Hoeks SE, et al. Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery. *Anesthesiology*. 2010;112:1316–1324.
15. Matyal R, Hess PE, Subramaniam B, et al. Perioperative diastolic dysfunction during vascular surgery and its association with postoperative outcome. *J Vasc Surg*. 2009;50:70–76.
16. Raevens S, De Pauw M, Geerts A, et al. Prevalence and outcome of diastolic dysfunction in liver transplantation recipients. *Acta Cardiol*. 2014;69:273–280.
17. Cho DH, Park SM, Kim MN, Kim SA, Lim H, Shim WJ. Presence of preoperative diastolic dysfunction predicts postoperative pulmonary edema and cardiovascular complications in patients undergoing noncardiac surgery. *Echocardiography*. 2014;31:42–49.

18. Chow S-C, Shao J, Wang H, Lokhnygina Y. *Sample Size Calculations in Clinical Research*. 2nd ed. New York, NY: Chapman & Hall/CRC; 2008.
19. Xu ZD, Xu HT, Li WW, Zou Z, Shi XY. Influence of preoperative diastolic dysfunction on hemodynamics and outcomes of patients undergoing orthotopic liver transplantation. *Int J Clin Exp Med*. 2013;6:351–357.
20. Shounak M, Vimal R, Colin S, David I S. A retrospective analysis of the impact of diastolic dysfunction on one-year mortality after transjugular intrahepatic porto-systemic shunt, liver transplantation and non-transplant abdominal surgery in patients with cirrhosis. *Ann Gastroenterol*. 2015;28:385–390.
21. Mittal C, Qureshi W, Singla S, Ahmad U, Huang MA. Pretransplant left ventricular diastolic dysfunction is associated with post transplant acute graft rejection and graft failure. *Dig Dis Sci*. 2014;59:674–680.
22. Higashi M, Yamaura K, Ikeda M, Shimauchi T, Saiki H, Hoka S. Diastolic dysfunction of the left ventricle is associated with pulmonary edema after renal transplantation. *Acta Anaesthesiol Scand*. 2013;57:1154–1160.
23. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet*. 2006;368:666–678.
24. Rao JY, Yeriswamy MC, Santhosh MJ, et al. A look into Lee's score: peri-operative cardiovascular risk assessment in non-cardiac surgeries-usefulness of revised cardiac risk index. *Indian Heart J*. 2012;64:134–138.
25. Siemelink M, den Ruijter H, van der Valk F, et al. Systemic glucocorticoids are associated with mortality after carotid endarterectomy. *J Cardiovasc Pharmacol*. 2015;66:392–398.
26. Moya FB, Pineda Galindo LF, García de la Peña M. Impact of chronic glucocorticoid treatment on cardiovascular risk profile in patients with systemic lupus erythematosus. *J Clin Rheumatol*. 2016;22:8–12.
27. Ajeganova S, Svensson B, Hafström I; BARFOT Study Group. Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: 10-year follow-up of a 2-year randomised trial. *BMJ Open*. 2014;4:e004259.