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Sex Differences in the Prevalence of Diastolic Dysfunction in Cardiac Surgical Patients

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Abstract

Objectives—The mortality from diastolic dysfunction is approximately 9% to 28%. In patients with ischemic heart disease, female sex and advanced age are associated with increases in ventricular diastolic stiffness. Clinical studies have found higher rates of diastolic dysfunction in women, despite higher ejection fractions, than in men post–myocardial infarction. Therefore, we hypothesized that female patients undergoing cardiac surgery have higher degrees of diastolic dysfunction and experience more adverse outcomes, such as prolonged hospitalization.

Methods—We prospectively enrolled 153 patients undergoing cardiac surgery. Diastolic function was assessed using early transmitral velocity (E) and early diastolic lateral mitral annular tissue velocity (e'). Left ventricular diastolic dysfunction was defined as binary and a continuous outcome (E/e').

Results—Females were more likely than males to present with higher E/e' (11.5 vs. 7.9, $p = 0.001$) and higher left ventricular diastolic dysfunction (71% vs. 36%, $p < 0.001$). The addition of sex to the model for left ventricular diastolic dysfunction was significant. The relationship between sex and E/e' ratio showed the biggest difference between males and females in the 56–72-year-old age brackets, where women were much more likely to have a higher E/e' than males.

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Conclusions—We identified a significantly higher prevalence of diastolic dysfunction among females presenting for elective cardiac surgery compared to males. This finding is more pronounced with age. Additionally, we found that female sex is at higher risk of prolonged ICU and hospital length of stay.

Over the last two decades, there has been a significant change in the prevalence of left ventricular diastolic dysfunction (LVDD), also known as heart failure (HF) with preserved ejection fraction (HFpEF). Clinical studies in the general population have shown that 40% to 71% of patients with HF have a preserved ejection fraction.^{1,2} The pathophysiology of HFpEF is distinct from that of HF with a reduced left ventricular ejection fraction (LVEF) and is characterized by impaired relaxation of myocardium, left ventricular stiffness, and, in many cases, increased arterial stiffness. Furthermore, the prognosis of patients suffering from left ventricular diastolic failure is similar to the patients presenting with systolic HF.³

LVDD is common in patients with coronary artery disease and has been shown to be associated with poor outcomes in patients undergoing cardiac surgery.⁴ Women undergoing isolated coronary artery bypass graft (CABG) surgery have an independently increased risk for postoperative morbidity and mortality. Recent studies in cardiac surgery have demonstrated that restrictive left ventricular filling emerged as a powerful predictor of mortality or major morbidity after CABG surgery, yet sex differences were not examined.⁵ Thus, we hypothesize that females presenting for cardiac surgery have a higher prevalence of LVDD than their male counterparts, and are more likely to experience adverse outcomes.

Materials and Methods

Patient cohort

We prospectively enrolled 153 consecutive patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) at Brigham and Women's Hospital between August 2010 and February 2011. With institutional review board approval, demographic data, medical and surgical history, intraoperative echocardiographic parameters, cardiac biomarker, and outcome data were recorded using defined protocols in a REDCap purpose-built electronic case report database. REDCap is an electronic data capture tool hosted by Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services group.⁶ Patients enrolled represented a standard mix of cardiac surgical procedures at our institution: primary CABG, CABG with mitral valve repair or replacement, and CABG with aortic valve replacement. For the analysis, we excluded patients with mitral stenosis, to prevent confounding of mitral inflow velocities by a mechanical obstruction rather than impaired relaxation.

All enrolled subjects underwent general anesthesia and surgery according to the standards of care at the Brigham and Women's Hospital. After induction of general anesthesia and central line placement, the transesophageal echocardiography (TEE) credentialed attending anesthesiologist assigned to the case performed and/or supervised the TEE examination. Assessment of diastolic function was performed according to the guidelines recommended by the Society of Cardiovascular Anesthesiologists and the American Society of Echocardiography.⁷

TEE assessment of diastolic function

Diastolic function was assessed and measured in real-time after induction of general anesthesia but before sternotomy. Accuracy of measurements was verified offline by an independent board-certified echocardiographer who was blinded to grading algorithm and outcome. Diastolic function was measured in the mid-esophageal four-chamber view by (i) transmitral inflow velocities using spectral pulsed wave Doppler; and (ii) velocities of the lateral mitral annulus using spectral tissue Doppler imaging. Spectral recordings were obtained at a sweep speed of 75 to 100 mm/sec at end-expiration and measurements were taken in 3 consecutive cardiac cycles and averaged. Diastolic function was assessed using an algorithm previously validated in a cardiac surgical patient cohort.⁴ It was based on the peak early transmitral flow velocity (E) and the early diastolic lateral mitral annular tissue velocity (e'), and graded according to Figure 1: normal (grade 0), impaired relaxation (grade 1), pseudonormal (grade 2), and restrictive (grade 3).⁸

Clinical end-points

The primary end-point was in-hospital mortality. The secondary end-points were intensive care unit length of stay (ICULOS), coded in hours, and hospital length of stay (HLOS), coded in days with the day of hospital admission and the day of discharge counting as full days. A defined protocol to transfer patients from the ICU and discharge from the hospital does not exist, yet the goal is always to move patients as quickly as their medical situation permits.

Statistical analysis

Left ventricular diastolic function was defined in two ways: first as a continuous variable using the E/ e' ratio as a measure of TEE stiffness and abnormal left ventricular (LV) filling pressures, which has been established previously in patients with cardiovascular disease;⁸ second, as a binary variable (grades 1–3 compared to grade 0; Fig. 1).

Demographic and procedural variables were compared between males and females using an unpaired *t*-test and the Wilcoxon rank-sum tests for continuous variables, and Chi square or Fisher's exact test for categorical variables, as appropriate.

To test our primary hypothesis that females presenting for cardiac surgery have a higher incidence of LVDD than their male counterparts, we created a multivariable logistic regression model with LVDD as the dependent binary variable (grades 1–3 vs. grade 0) and a multivariable linear regression model with a continuous E/ e' as the outcome. In both models, we adjusted for demographics and clinical covariates, including age, sex, body mass index, preoperative creatinine and left ventricular ejection fraction, hypertension, left atrial volume index, MAZE procedure, type of surgical procedure, and presence of coronary artery disease. A *p* value of less than 0.05 was considered statistically significant. All analyses were conducted using JMP Pro (Version 11.0.0, SAS Inc., Cary, NC, USA).

HLOS and ICULOS were estimated by Kaplan–Meier analysis and comparison of survival curves was carried out with the nonparametric log-rank test. The association between the clinical end-points was assessed using a nominal logistic regression model for mortality and

a Cox proportional hazard model for HLOS and ICULOS. These models were created by entering clinically relevant covariates into the model based on a priori background knowledge. Since we considered that preoperative E/e' might mediate the association between sex and HLOS or ICULOS, we did not include preoperative E/e' variable in the final adjusted model. The final model included body mass index, preoperative creatinine, CPB time, age, preoperative ejection fraction, and sex. Because we were also interested in measuring the magnitude of the direct effect of sex which is not mediated by the preoperative E/e', we performed a direct effect model, including preoperative E/e' as a continuous variable under the assumption that upon adjusting for observed covariates, no unobserved confounding remained for the joint effects of sex and the preoperative E/e', on HLOS or ICULOS. We also assumed that the sex did not confound the relationship between preoperative E/e', on HLOS or ICULOS. For HLOS, patients who died during their primary hospitalization were censored; those who stayed 30 days or longer were counted as having a truncated HLOS of 30 days. For ICULOS, patients who died while in the ICU were censored. We checked the proportional hazards assumption with cumulative sums of martingale-based residuals.

Power analysis

To calculate the sample size required to be adequately powered to detect significant differences in LV stiffness between males and females, we used data from our previous retrospective study (unpublished) to assume a standardized effect size difference of 0.5 between the groups, as per Cohen's *d*. We prospectively enrolled patients and due to the inherent nature of our cardiac surgical patient population, two out of three are usually male. So for our power analysis, we calculated a 2:1 ratio of males to females, which revealed that 144 patients (96 males and 48 females) were required to assess a difference of 0.5 in E/e' between the groups as significant with 80% confidence using a *t*-test and assuming a two-tailed alpha of 0.05 (G*Power 3.1.2: Kiel, Germany).⁹

Results

Demographic and procedural variables are described in Table 1. The patients had a mix of cardiac surgical procedures: 32 (21%) had isolated CABG surgery, 48 (31%) had CABG + valve surgery, 68 (44%) had valve surgery, and five (3%) had aortic surgery.

Sixty-one patients (40%) had normal diastolic function according to our grading algorithm in Figure 1, while 19 (12%) had grade 1, 41 (27%) had grade 2, and 32 (21%) patients had grade 3 LVDD.

For the primary hypothesis, females were more likely to present with higher E/e' (11.5, interquartile range [IQR 8.0–15.0] vs. 7.8 [5.9–10.9], *p* = 0.001) and higher LVDD (71% vs. 36%, *p* < 0.001) compared to males (Fig. 2). After adjusting for important clinical covariates and demographics in the multivariable model with diastolic LV stiffness defined as a continuous variable, female patients had a significantly higher E/e' ratio compared to males (*p* < 0.01; Table S1). In addition, female patients were also significantly more likely to present with a higher grade of LVDD compared to men after covariate adjustment (odds ratio (OR) = 4.69 [1.84–11.96], *p* = 0.001; Table 2). The addition of sex to the model for

LVDD was significant. The relationship between sex and E/e' ratio in five different age groups shows the biggest difference between males and females in the 56–72-year-old age brackets, where women were much more likely to have a higher E/e' than males (Fig. 3).

Clinical end-points

Bivariate analyses—In bivariate analysis, the median HLOS between males and females was significantly different ($p = 0.05$), while ICULOS was not ($p = 0.13$) (Table 1). A Kaplan–Meier survival analysis showed a significant difference between males and females on their duration of HLOS ($p = 0.038$; Fig. 4).

Patients who died in the hospital were not more likely to be female ($p = 0.62$), have a higher E/e' ($p = 0.11$) or LVDD ($p = 0.24$).

The E/e' ratio was significantly associated with prolonged ICULOS ($r^2 = 0.04$; $p = 0.009$), but not HLOS ($r^2 = 0.02$; $p = 0.086$). Despite a slight increase in median ICULOS and HLOS in patients with LVDD, the association was not significant (ICULOS $p = 0.318$; HLOS $p = 0.232$).

Multivariable analyses—The risk of prolonged HLOS (inversed hazard ratio [IHR] 2.27 [1.55–3.32], $p = 0.001$; Table 3) and ICULOS (IHR 1.73 [1.20–2.49], $P = 0.017$; Table S2) was almost twice as high for female patients. We found that the effect of sex on the HLOS or ICULOS in the direct effect model was smaller than the marginal effect (IHR = 2.11 versus 2.27 for HLOS; IHR = 1.58 vs. 1.73 for ICULOS; Table 3 and Table S2).

With only seven deaths (4.6%) during hospitalization, neither sex nor LVDD or E/e' were significant predictors of in-hospital mortality. Analyses of cumulative sums of martingale-based residuals showed that the proportional hazard assumptions held in all Cox's models.

Conclusions

In a prospective cohort of cardiac surgical patients, we investigated the association between sex and diastolic function, and the effect of both on short-term clinical outcomes and mortality. Using intraoperative TEE, we validated our primary hypothesis, that female patients presenting for elective cardiac surgery have significantly worse intraoperative diastolic dysfunction, assessed by examining LV stiffness using E/e' and a binary variable of LVDD. In addition, LV stiffness increased significantly more with age in females than males, and females were more likely to have prolonged ICU and HLOS.

In clinical studies, the prevalence of LVDD in females has been well determined; older women represent over 75% of patients diagnosed with HFpEF.^{1–4} However, the pathophysiology of LVDD in women has yet to be defined. Recent animal studies concluded that loss of activation of endogenous hormonal receptors in the heart could provoke deposition of interstitial collagen and myocardial hypertrophy, ultimately leading to LVDD.⁵ These findings indicate that hormonal changes might play a role in the development of LVDD in the female population.

Diastolic dysfunction is prevalent in patients with coronary artery disease, and is associated with poor outcomes in cardiovascular surgery.^{10,11} Furthermore, diastolic dysfunction is common in patients with HF.¹² Large clinical studies examining sex difference on the prevalence of HF, particularly HFpEF, have demonstrated that it is more common among women.² In a recent study of older patients with Stage 1 hypertension, women appeared to have more impaired left ventricular diastolic function and higher estimated filling pressure than men assessed by E/E' and E' .¹³ These findings can even be extended to older patients without cardiovascular disease where it has been shown that women have slower left ventricular relaxation,¹³ increased left ventricular stiffness,¹⁴ and a greater decline in long-axis velocities during diastole.¹⁵

There is a growing recognition of sex-related differences in outcomes among patients with ischemic heart disease.¹⁶ The operative mortality of females undergoing CABG is found to be considerably higher when compared to men, with most series reporting a female mortality approximately twice that of men.^{17,18} This was further supported by data from the National Cardiovascular Network database, where females undergoing CABG surgery were found to have higher mortality when compared to males. One could postulate that the clinical presentation differs from females to males, especially in females <65 years, which is confirmed by examining the US National Registries of Myocardial Infarction, in which young women are more likely than men of similar age to present without chest pain.¹⁹

Multiple studies demonstrated that LVDD was valuable in predicting outcome in patients undergoing cardiac surgery.^{4,20} Diastolic dysfunction predicted increased adverse events, including mortality, regardless of LVEF. Additionally, female patients undergoing isolated CABG surgery had a greater 30-day mortality, though this was possibly due to a higher preoperative risk factor profile.²¹ This was confirmed in our study where, despite a similar pre-operative risk profile and significantly longer CPB and aortic cross-clamp times for females, we found a significantly higher risk of prolonged HLOS and ICULOS in females undergoing cardiac surgery. The correlation between LVDD and higher mortality was not confirmed, though this was likely due to the small number of deaths in our cohort.

To date, there are currently no specific therapies for diastolic dysfunction or prevention of its occurrence in patients undergoing cardiac surgery approved in the United States. Levosimendan, a calcium sensitizer and approved for use in Europe, has been shown to exert a direct positive lusitropic effect in patients with LV hypertrophy as it shortens isovolumic relaxation time and improves LV filling.²² The findings of our study might suggest that some changes in clinical practice, such as preoperative hormonal replacement in postmenopausal females with LV diastolic dysfunction, might have an impact on hospital and ICULOS in the setting of females undergoing cardiac surgery.

Limitations

We understand that one of the limitations of the study is the lack of assessment of diastolic function with preoperative transthoracic echocardiography and the use of intraoperative TEE. However, since we are not using quantitative analysis to make a diagnosis but rather are comparing females to males at the same time point in the operation, the comparison

between sexes appears valid. In addition, we did not assess hormone replacement therapy in postmenopausal patients, which could have altered the incidence of LVDD and confounded our results. Yet, because there is a lack of clinical evidence correlating estrogen-based therapy and cardiovascular events, we believe that our findings would not be significantly different if we included data on preoperative hormone therapies in our patients. We also did not examine the association between 3-hydroxy-3-methylglutaryl-coenzyme A HMG-CoA reductase inhibitors and diastolic dysfunction.

In summary, we identified a significantly higher prevalence of diastolic dysfunction among females presenting for cardiac surgery compared to males. We also demonstrated an age association, with younger women presenting with higher E/e', which confirms preclinical animal models. Additionally, we found a significant relationship between diastolic dysfunction and short-term adverse outcomes. The etiology of these findings that women paradoxically have worse degrees of LVDD compared to men after cardiac surgery, despite having less severe coronary artery disease, remains unclear, yet it confirms studies in non-surgical populations. A better understanding of the risk factors associated with increased diastolic dysfunction in women might lead to the development of new strategies for prevention, detection, and management during the perioperative period of this vulnerable patient group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Algorithm used for grading diastolic dysfunction. TDI, tissue Doppler imaging.

Figure 2. Distribution of the E/e' by sex. Box-whisker-plot showing box with median E/e' with edge of boxes at 25–75%, whiskers extending 1.5× the interquartile range, and outliers represented with dots.

Figure 3.

A contour analysis graph showing the relationship between left ventricular stiffness and sex. The shape of the figures represents the number of patients within each age group and their respective E/e'. Females are much more likely to have a higher E/e' than males.

Figure 4.

Kaplan–Meier analysis HLOS in 30 days. This graphic demonstrates the female versus male sex HLOS in 30 days ($p = 0.038$). HLOS, hospital length of stay.

Table 1
Demographic and Operative Characteristics

Variable	(N = 153)		
	Females (N = 52)	Males (N = 101)	P-value
Age (years)	72 (61–83)	67 (58–77)	0.06
Hypertension, N (%)	39 (75)	64 (63)	0.20
Weight (kg)	68.8 (60.0–82.8)	84.0 (76.9–93.0)	<0.01
Left ventricular ejection fraction (%)	60 (50–60)	60 (50–60)	0.67
Preoperative creatinine (mg/dL)	0.96 (0.8–1.1)	1.0 (0.9–1.2)	0.08
Cardiopulmonary bypass time (minute)	122 (97–150)	159 (107–209)	<0.01
Aortic cross-clamp time (minute)	82 (71–105)	112 (79–153)	<0.01
Baseline E/e' ratio	11.5 (8.0–15.0)	7.8 (5.9–10.9)	<0.01
LVDD (grade 1–3 vs. 0) (%)	43 (83)	49 (49)	<0.01
BMI	26.9 (22.8–32.0)	27.3 (25.2–30.8)	0.25
MAZE, N (%)	2 (4)	10 (10)	0.22
Coronary artery disease, N (%)	33 (63)	77 (76)	0.13
Type of surgery — AVR versus TVR or MVR	34 (65)	69 (68)	0.72
Left atrial volume index (mL/m ²)	29.8 (22.6–39.8)	29.7 (20.1–41.4)	0.90
ICU length if stay (hours)	48.8 (39.4–91.5)	45.3 (26.2–72.4)	0.13
Hospital length of stay (days)	7 (6–12)	7 (6–9)	0.05

Values are expressed as median with interquartile range, unless specified otherwise. AVR, aortic valve replacement; BMI, body mass index; ICU, intensive care unit; LVDD, left ventricular diastolic dysfunction; MVR, mitral valve replacement/repair; TVR, tricuspid valve replacement/repair. P-values are Wilcoxon rank sums or two-tailed Fisher's exact as appropriate.

Table 2
Multivariable Logistic Regression Model of Variables Independently Associated with Diastolic Dysfunction

Variable	Odds Ratio (95% CI)	P-Value
Female sex	4.69 (1.84–11.96)	0.001
Age	1.07 (1.03–1.11)	<0.001
Body mass index	0.96 (0.89–1.03)	0.37
Preoperative creatinine	1.20 (0.46–3.09)	0.71
MAZE procedure	0.21 (0.04–1.16)	0.07
Preoperative LVEF	0.99 (0.94–1.03)	0.49
LA volume index (ml/m ²)	0.99 (0.97–1.02)	0.61
Hypertension	1.50 (0.62–3.63)	0.37
Type of valve surgery	1.35 (0.49–3.70)	0.56
Coronary artery disease	0.76 (0.25–2.29)	0.63

Diastolic dysfunction defined as binary variable (grades 1–3 [N = 92] vs. 0 [N = 61]; see text for details). C-statistics = 0.824. Hosmer and Lemeshow test: P-value = 0.6485. LA, left atrium; LVEF, left ventricular ejection fraction; Type of valve surgery = aortic valve replacement versus mitral or tricuspid valve replacement/repair.

Table 3
Cox Proportional Hazard Model of Hospital Length of Stay

HLOS	Final Model		Direct Effect Model	
	IHR (95% CI)	P-Value	IHR (95% CI)	P-Value
BMI (per ten kg/m ²)	1.17 (1.01–1.35)	0.032	1.19 (1.02–1.38)	0.027
Preoperative creatinine	1.42 (1.00–2.03)	0.053	1.58 (1.02–2.44)	0.04
CPB duration (per ten minutes)	1.05 (1.02–1.07)	<0.001	1.05 (1.02–1.08)	<0.001
LVEF preop (per 10% increase)	0.78 (0.66–0.93)	0.006	0.77 (0.63–0.92)	0.005
Sex (female)	2.27 (1.55–3.32)	<0.001	2.11 (1.55–3.32)	<0.001
Age (per decade)	1.27 (1.12–1.43)	<0.001	1.23 (1.09–1.40)	0.001
Pre E/e' (per ten unit increase)	–	–	1.44 (1.02–2.01)	0.033

Demographic and clinical variables shown in model columns are included in the analyses. Hospital length of stay is modeled as Cox proportional hazard model. HLOS is a continuous outcome measured in days. IHR, inversed hazard ratio; BMI, body mass index; CI, confidence interval; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; Pre E/e', diastolic dysfunction defined as a continuous variable (see text for details). P-values expressed using Wald test. Harrell's c-statistics: final model = 0.328; direct effect model = 0.317.