Diastolic Dysfunction in Patients Undergoing Cardiac Surgery: The Role of Gender and Age-Gender Interaction

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Objectives: To test the hypothesis that females presenting for coronary artery bypass graft (CABG) surgery are at a higher risk of left ventricular diastolic dysfunction (LVDD) and that age and gender interact to influence this risk.

Design: Retrospective observational study.

Setting: Tertiary university hospital.

Participants: Eight hundred-ninety-five adult patients undergoing CABG surgery.

Interventions: None.

Measurements and Main Results: Baseline diastolic function was graded according to a predefined Doppler-based algorithm, which defined LVDD as a binary variable (grades 2 and 3 only) and as a continuous variable (E/e' ratio). The authors found that women were more likely to present with LVDD in 2 multivariate regression models using both LVDD definitions (odds ratio = 2.7; $p < 0.0001$ for logistic model, and parameter estimate (PE) = 2.8; $p < 0.0001$ for the linear model). In addition, there was a significant age and gender interaction on the risk of LVDD in the linear model (PE = 0.08; $p = 0.01$). A restricted cubic splines analysis revealed a progressively higher risk of LVDD (predicted E/e' ratio) among older women.

Conclusions: The authors confirmed that women undergoing CABG surgery are at higher risk of LVDD compared to men with a significant age-gender interaction suggesting a possible age-related differential effect on LVDD between the genders, a phenomenon previously demonstrated in preclinical studies. Therapies aimed at amelioration of diastolic dysfunction additionally should consider the higher risk in females, especially within the older subset of the patient population.

KEY WORDS: coronary artery disease, diastole, surgery, women, aging, diastolic dysfunction

LEFT VENTRICULAR DIASTOLIC DYSFUNCTION (LVDD) refers to an abnormality of diastolic distensibility, filling, or relaxation and is an important determinant of cardiovascular function. Indeed, LVDD is the predominant abnormality in patients with heart failure with preserved ejection fraction (HFpEF), which comprises approximately half of the patients with heart failure.[1,2] In contrast to heart failure with reduced ejection fraction, the incidence of HFpEF has increased over the years and if these trends persist, HFpEF may become the most common type of heart failure in the near future.[1,3] Studies indicate that women are at higher risk for developing HFpEF compared to men.[4] Investigators have also shown that gender and age-gender interaction may play a role in the pathogenesis of LVDD.[5,6] Possible mechanisms are changes in the hormonal milieu that accompany normal aging, which subsequently contribute to the development of hypertension and left ventricular hypertrophy and predispose women to a higher risk of LVDD.[7]

Left ventricular diastolic dysfunction also is common in patients with ischemic heart disease and has been shown to be associated with long-term adverse outcomes in patients undergoing coronary artery bypass grafting (CABG) surgery.[8] Similar to their risk for developing HFpEF, women also have a higher risk for morbidity and mortality following CABG than their male counterparts.[9] However, there are limited perioperative data on the association among gender, age, and LVDD in cardiac surgery patients. The authors, therefore, conducted a study to determine the association between gender and LVDD in the setting of CABG surgery. The authors tested the hypothesis that females undergoing CABG surgery are more likely than male patients to present with LVDD. The authors further hypothesized that age and gender interact to influence this risk.

METHODS

With approval from the authors' institutional review board, detailed clinical and intraoperative transesophageal echocardiographic data were analyzed in a cohort of 897 adult patients undergoing elective, isolated CABG surgery with CPB at Duke University Medical Center in whom complete intraoperative TEE data had been acquired in order to allow diastolic function grading. Patients who were determined by the clinical care team to be hemodynamically unstable, or had any arrhythmia were excluded. Patients dependent preoperatively on electrical pacing, inotropes, or intra-aortic balloon pump support also were excluded. Anesthesia and surgery were conducted based on an institutional protocol, which previously has been described.[8]

Data were extracted from the Duke Databank for Cardiovascular Diseases, a large, quality-assured database that prospectively gathers demographic, periprocedural, and followup data for all cardiovascular interventions performed at Duke University.

Measurements pertaining to diastolic function were obtained at baseline after induction of general anesthesia. All measurements were made in real time and their accuracy verified offline by an independent, board-certified echocardiographer who was blinded to grading algorithm and outcome. Assessment of LV diastolic function was performed using a previously–described, simplified algorithm based on the peak early transmitral flow velocity (E) and early diastolic velocity of the lateral mitral annulus (e'). Diastolic function was defined in 4 grades: Normal (grade 0), impaired relaxation (grade 1), pseudonormal (grade 2), and restrictive (grade 3) as shown in Figure 1.

Diastolic dysfunction was defined in 2 ways. First, as a binary variable (grades 2 or 3 only), and second, as a continuous variable using the E/e' ratio as a measure of LV stiffness. While grades 0 and 1 were considered to reflect normal left atrial pressure, grades 2 (pseudonormal) and 3 (restrictive filling) reflected elevated left atrial

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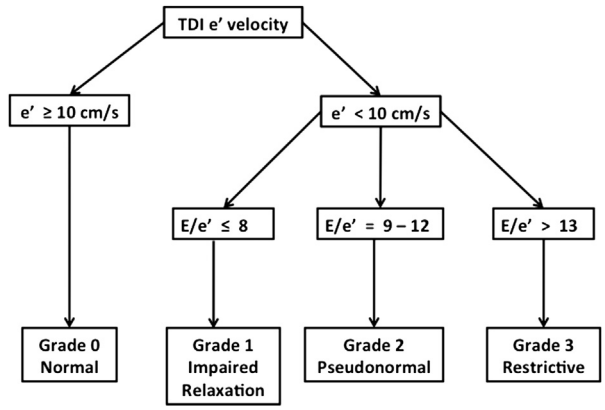

Fig 1. Algorithm used for grading diastolic dysfunction. Abbreviations: TDI, tissue Doppler imaging.

pressure and were therefore categorized together as LVDD for the binary outcome. The E/e' ratio is an established marker of abnormal LV filling pressures in patients with cardiovascular disease.[10]

Demographic and procedural variables were compared between the 2 gender groups using analysis of variance (ANOVA) and the Wilcoxon rank-sum tests for continuous variables and Chi square or Fischer's exact test for categoric variables as appropriate.

For the authors' primary hypothesis, a multivariate logistic regression model was developed with LVDD as the dependent binary variable (grades 2 or 3 only) and female gender as the principal independent variable of interest. A second multivariate linear regression model was developed to test the independent association between female gender and E/e'. In both models, the authors adjusted for age, congestive heart failure, weight, diabetes, hypertension, LV ejection fraction, and cardiopulmonary bypass time.

For the secondary hypothesis, the authors investigated the interaction between age and gender and their association with diastolic dysfunction by adding the 'age-gender' interaction term to both regression models. For further descriptive purposes, the authors employed a restricted cubic spline analysis that allowed them to explore the possibility of nonlinear relationships between age and the E/e' ratio. The inclusion of the interaction term (age * gender) allows the slopes of the lines to vary between males and females. The spline analysis allows the smoothed fitted line to vary in slope at predetermined points and is constrained to be linear in the tails. The location of the splines, or knots (the points at which the slope of the line is free to vary) were chosen based on recommended quantiles described by Harrell.[11] Predicted values were produced from the multivariate model, which was adjusted for the same covariables as in the primary analysis. The predictors of interest for the purpose of this analysis were age and gender and their interaction.

A p value of less than 0.05 was considered statistically significant. All analyses were conducted using SAS statistical software (Version 9.1.3, SAS Inc, Cary, NC).

RESULTS

Demographic and procedural variables for the cohort of 895 patients are described in Table 1. There were 158 patients (18%) with normal diastolic function while 309 (34%) had grade 1, 207 (30%) had grade 2, and 161 (18%) patients had grade 3 LVDD. Statistically significant differences between the two genders were noted in several variables as shown in table 1. A greater proportion of females were Caucasian (27 vs. 16%). Female patients were also older (66 vs. 63 years), had higher rates of diabetes (44 vs. 32%), and chronic obstructive pulmonary disease (18 vs. 11%) compared to male patients. In addition, females had a lower average body weight (83 vs. 92 kg), and a lower average left ventricular ejection fraction (50 vs. 53%). Significant differences in diastolic function variables were also noted. Female patients had a higher average baseline E/e' ratio (11.5 *v* 8.3) and a correspondingly higher percentage of cases with grades 2 or 3 LVDD (68 *v* 41%), indicating worse baseline diastolic function in this subset of patients.

The authors' primary hypothesis was confirmed in both multivariable models that defined LVDD as a binary variable and LV diastolic stiffness (E/e') as a continuous variable. Female patients were more likely to present with LVDD defined as a binary variable (odds ratio = 2.73; 95% confidence interval = 1.9-3.8; $p < 0.0001$) (Table 2). Female gender remained significantly associated with E/e' in the linear regression model (parameter estimate = 2.78; $p < 0.0001$) (Table 3). Other significant co-variables were age, diabetes and low ejection fraction.

For the secondary hypothesis, the addition of the age-gender interaction term to the logistic regression model showed marginal significance. (Linear regression model showed that there was a significant association between age-gender and E/e' (parameter estimate = 0.08; $p = 0.01$).

The results of the restricted cubic spline analysis of the interaction between age and gender and their association with diastolic dysfunction are shown in Figure 2. The specific ages that are knots (the points at which the lines are free to vary) in this analysis are 80, 72, 65, 57, and 47. The risk in diastolic dysfunction increases in slope between 60 and 70 for both males and females but is steeper in females and does not reach a plateau as it does in males.

Table 1. Demographic and Operative Characteristics

Variables	Females (n = 236)	Males (n = 661)	p Value
Age (years)	66.6 (10.0)	63.3 (10.2)	<0.0001
Caucasian (%)	26.7	15.8	0.0002
Congestive heart failure (%)	18.5	17.6	0.74
Hypertension, n (%)	77.6	74.8	0.40
Diabetes mellitus (%)	44.0	32.2	0.001
Weight (kg)	83.4 (23.2)	92.1 (20.8)	<0.0001
Left ventricular ejection fraction (%)	49.9 (14.9)	53.3 (13.6)	0.02
Preoperative creatinine (mg/dL)	1.2 (1.1)	1.3 (1.2)	0.33
COPD (%)	18.1	11.3	0.008
Previous MI (%)	18.7	39.7	0.12
EuroSCORE	9.2 (3.0)	8.1 (3.3)	<0.0001
Cardiopulmonary bypass time (min)	128 (61)	124 (42)	0.38
Aortic cross-clamp time (min)	72 (25)	71 (23)	0.90
Baseline E/e' ratio	11.5 (5.8)	8.3 (4.1)	<0.0001
LVDD (grade 2 or 3) (%)	67.7	40.9	<0.0001

NOTE. Values are expressed as mean with standard deviation in parentheses unless specified otherwise. The p values are Wilcoxon rank sums or 2-Tailed Fisher's exact test as appropriate.

Abbreviations: COPD, chronic obstructive pulmonary disease; LVDD, left ventricular diastolic dysfunction; MI, myocardial infarction.