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Familial dilated cardiomyopathy diagnosis is commonly overlooked at the time of transplant listing

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Abstract

BACKGROUND—The prevalence and clinical characteristics of familial dilated cardiomyopathy (FDCM) among patients with end stage heart failure (ESHF) has yet to be elucidated. We sought to determine the prevalence of FDCM in ESHF in the United Network for Organ Sharing (UNOS) registry and compare this with center specific data from a large tertiary teaching hospital. Patients with a banked UNOS diagnosis of dilated cardiomyopathy (DCM) whose care originated at our center then underwent detailed pedigree analysis in order to determine the true prevalence of FDCM.

METHODS AND RESULTS—A total of 16,091 patients with DCM from all centers were identified in the UNOS registry of whom 492 carried the diagnosis of FDCM (3.1%). Patients with the diagnosis of FDCM tended to be younger (42 versus 49 years old in idiopathic dilated cardiomyopathy (IDCM), $p=0.001$), were less likely to have diabetes (7.8% versus 16.5% in IDCM, $p<0.0001$), had slightly lower creatinine (1.2 versus 1.4 in IDCM, $p=0.0001$) and were more likely to have a panel reactive antibody level $\geq 20\%$ (62.1% versus 44.7% in IDCM, $p<0.0001$). Consecutive living adult patients with ESHF were identified from the UNOS registry that had been treated at the Yale Center for Advanced Heart Failure (YCAHF). After excluding all diagnoses that did not include any form of non-ischemic DCM, 73 patients met the inclusion criteria. Center-specific UNOS data showed pre-pedigree analysis diagnosis of FDCM in 4.12% of patients (3 out of 73), consistent with that found in the UNOS database for all centers. However, after detailed family history and pedigree analysis, 19 (26%) of 73 patients were found to have FDCM, while the remaining 54 were found to have IDCM. Echocardiographic findings including mitral regurgitation, mitral valve annulus and left ventricular end diastolic dimension were not significantly different between groups when adjusting for multiple testing.

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Disclosure statement

None of the authors of this manuscript have financial conflicts of interest to disclose.

CONCLUSIONS—The diagnosis of FDCM was missed in the majority of patients with end stage heart failure enrolled in the UNOS database, as sampled from a large, tertiary care teaching hospital in the United States. Echocardiographic findings are unlikely to aid in the differentiation between DCM and FDCM. Detailed pedigree analysis can successfully identify undiagnosed FDCM and should be encouraged prior to transplant listing as it has important implications for early detection and treatment of disease in family members.

Keywords

cardiomyopathy; familial dilated cardiomyopathy; end-stage heart failure; pedigree analysis

Introduction

One of the most commonly stated indications for orthotopic heart transplant (OHT) is idiopathic dilated cardiomyopathy (IDCM), which typically presents as systolic impairment and dilatation of the left ventricle. As outlined by both the AHA and European Consortium consensus documents, ischemic etiology is excluded from the diagnosis of IDCM (in approximately 50% of cases). Other secondary causes of LV dilatation and dysfunction should be considered and if none are identified, other than familial inheritance, then the diagnosis of IDCM is reached. Depending on diagnostic methods, in stable non-ischemic heart failure (HF) populations, familial dilated cardiomyopathy (FDCM) is estimated to have a prevalence of 25–50%.^{1–4} The burden of FDCM in end-stage heart failure (ESHF) was previously investigated in Spanish cohorts and indicated prevalences of 25%⁵ and 19%.⁶ However, the Spanish cohorts may have been selectively enriched with FDCM patients secondary to population homogeneity and consanguinity. Because of this lack of clarity, we sought to investigate the prevalence of FDCM in a national registry and compare it to center specific data in a heterogeneous US cohort of ESHF patients to determine the prevalence of FDCM among ESHF patients. Moreover, we sought to determine whether current approaches for screening of FDCM are effective in ESHF. Finally, we sought to determine whether clinical and echocardiographic parameters reliably defer between FDCM and IDCM in end stage disease.

Methods

Center-specific

Consecutive living adult patients with ESHF that had received their care at YCAHF were screened from the UNOS registry (Figure 1). For the purposes of this study ESHF was defined as requirement for OHT or placement of a left ventricular assist device (LVAD) as bridge to OHT. Of note, data from every patient undergoing OHT or LVAD placement as a bridge to OHT in the United States are banked into the UNOS registry. Upon entry into the UNOS registry, input of a diagnosis is required. In this paper we refer to the diagnosis input at the time of patient entry into UNOS as the UNOS diagnosis. Patients whose UNOS diagnoses included non-ischemic DCM were included in the study (DCM: Idiopathic, DCM: Myocarditis, DCM: Other, DCM: Post Partum, DCM: Familial, DCM: Adriamycin, DCM: Viral, DCM: Alcoholic). These diagnoses were all included in order to test our hypothesis that familial DCM is under diagnosed and frequently mistaken for other forms of non-

ischemic DCM. All other UNOS diagnoses were excluded including ischemic CM, hypertrophic CM, restrictive myopathy, congenital heart disease and valvular heart disease. After obtaining informed consent, (HIC 1005006865), detailed pedigrees (3-generation minimum) were then obtained on all study subjects. Based on pedigree analysis, patients were assigned to one of the following groups: confirmed FDCM, probable FDCM, possible FDCM, or IDCM using stringent criteria similar to previously published reports (Figure 1).⁷ FDCM was a priori defined as meeting criteria for confirmed or probable FDCM. The diagnosis of IDCM was assigned to patients with possible FDCM, no FDCM, and to those meeting inclusion criteria but who were unable or unwilling to participate (in order to avoid enrichment bias of patients that may more motivated to participate if they have a family history).

National

In a separate analysis, UNOS registry (as of December 31, 2010) was interrogated to determine prevalence of FDCM in end-stage non-ischemic DCM. UNOS diagnoses of non-ischemic DCM are described above.

Echocardiography

The most recent echocardiogram prior to OHT or LVAD placement was used for analysis. Available echocardiographic data (53 patients) were reviewed by a research sonographer and a board certified echocardiographer blinded to patient diagnosis. Discrepancies in analysis were adjudicated through combined review. Because echocardiographic data were obtained over many years in a clinical setting there was no standardization of echo machine use across the population. Parameters assessed included: mitral regurgitation, mitral valve annulus dimensions, LV EDD, LVEF, left atrial volume & index, RV basal diameter, RV fractional area change, right atrial area.

Statistical analysis

Patient demographic and clinical characteristics of the YCAHF cohort obtained from UNOS were compared by status of FDCM or DCM. For continuous variables, the mean and SD were calculated, and for categorical variables, proportions or percentages were calculated. For unadjusted comparisons between groups, the Kruskal-Wallis rank test was used for continuous variables, and the χ^2 test was used for categorical variables. Statistical analysis for echocardiographic data was performed using Kruskal-Wallis rank test for continuous variables and chi-squared for categorical variables.

Results

UNOS registry

A total of 16,091 patients with DCM were identified in the UNOS database (Table 1). Of those, 492 carried the diagnosis of FDCM (3.1%) (Table 1 and Table 2). Patients with the diagnosis of FDCM tended to be younger (42 versus 49 years old in IDCM, $p=0.001$), were less likely to have diabetes (7.8% versus 16.5% in IDCM, $p<0.0001$), had slightly lower creatinine (1.2 versus 1.4 in IDCM, $p=0.0001$) and were more likely to have a panel reactive antibody (PRA) level $\geq 20\%$ (62.1% versus 44.7% in IDCM, $p<0.0001$) (Table 1).

Percentage of males was slightly less in FDCM and white race was more prevalent in FDCM versus IDCM but both were not statistically significant after correcting for testing multiple variables. There were no differences between COPD, prior cardiac surgery, BMI, smoking history and dialysis between the FDCM and IDCM groups (Table 1).

FDCM was further broken down by year of diagnosis to illustrate the prevalence over time (Table 2). In 1990–1994 the percentage of FDCM was 1.5% of all DCM in those years, 2.2% in 1995–1999, 3.1% in 2000–2004, and 5.3% in 2005–2010.

Center specific data from the UNOS registry

Seventy-three patients met inclusion criteria for the center specific study. Two declined to participate and 8 were unable to be reached. Sixty-three patients ultimately underwent pedigree analysis.

Center-specific UNOS data revealed diagnosis of FDCM in 3 out of 73 (4.12%) patients (Figure 2) similar to the prevalence of 3.06% in the overall UNOS dataset. The prevalence of other UNOS diagnosis prior to pedigree analysis were: 49 IDCM; 3 peripartum DCM; 2 adriamycin induced cardiomyopathy; 1 viral cardiomyopathy; and 4 DCM-other. After pedigree analysis 19 (26%) patients were found to have FDCM (Figure 2) (10 confirmed FDCM, 9 probable FDCM). The remainder (54) patients were found to have IDCM by study definitions (9 possible FDCM and 45 IDCM). Of note, patients who declined to participate or who were not reachable¹⁰ were placed in the IDCM group to avoid selection bias (Figure 2).

Significant family history elicited from those subjects with diagnoses of “confirmed” or “probable” FDCM following 3-generation pedigree analysis are listed in Table 3. A subset of these subjects underwent genetic testing (limited by insurance reimbursement and patient preference). Results of genetic testing are listed in Table 3. Five of ten “confirmed” or “probable” FDCM subjects that underwent genetic testing had pathogenic or likely pathogenic mutations identified; one of the ten had a variant of unknown significance; the remaining four had negative genetic analysis.

Further characterization of the Yale cohort is presented in Table 4. Age, gender, race, BMI, atrial or ventricular arrhythmias and conduction disease did not significantly differ between FDCM versus IDCM groups. Skeletal myopathy was present in two FDCM patients (one was a carrier of an LMNA mutation and the other with a history of familial myotonic dystrophy) versus in none of the IDCM patients ($p=0.02$).

Echocardiography

Of 73 patients included, 53 had echocardiograms available for review (39 IDCM, 14 FDCM). Left atrial volume (LAV) and LAV-index were significantly increased in the IDCM cohort. Increased mitral regurgitation, left atrial volume and left atrial volume index ($p=0.044$, 0.045 , 0.008 respectively) were noted among the FDCM cohort, although this was not significant after adjusting for multiple testing. There was no significant difference in LV EDD ($p=0.64$) or mitral annular measurement. There was a trend towards worse RV FAC in IDCM patients but this also failed to achieve statistical significance ($p=0.053$) (Table 4).

Discussion

This study describes the prevalence and characteristics of FDCM in the National UNOS registry. It suggests that FDCM accounts for a significant proportion of end-stage non-ischemic DCM patients (26%) listed for heart transplantation in a heterogeneous patient population. It further suggests that the majority of FDCM is undiagnosed at the time of transplant listing. In the national cohort, FDCM patients tended to be diagnosed with ESHF at a younger age, were less likely to have diabetes, had slightly better renal function and higher PRA. These findings are consistent with primary inherited cardiomyopathy unrelated to other underlying disease. The presence of higher PRA in FDCM is intriguing suggesting that enhanced immunologic activity may play a role in disease development for this cohort. While we were unable to identify echocardiographic characteristics that reliably distinguished between IDCM and FDCM, development of a 3-generation pedigree and application of a simple scoring system readily identifies individuals and families at increased DCM risk. Since the diagnosis of FDCM yields actionable information (family screening), additional research will be necessary to validate these findings and determine how more effective screening can be implemented.

Diagnosis at the time of advanced therapy evaluation

Pre-existing conditions that can lead to DCM are many and the etiology of HF is typically a rule out phenomenon owing to lack of clear phenotypic or histopathologic pathognomonic traits for many of these diagnoses. Many patients presenting for heart failure will have a history of one of the following: hypertension, diabetes, alcohol use, prior viral illness, and pregnancy. Therefore, the diagnoses of hypertensive, diabetic, alcoholic, peripartum, and viral cardiomyopathy are frequently utilized to explain etiology. Though family history is, presumably, a routine portion of the intake procedure for patients referred for heart transplantation, a detailed 3-generation pedigree is rarely constructed, and the criteria upon which to judge the pedigree are not widely known by heart failure cardiologists. Further, studies have indicated that the majority of affected family members with FDCM may be asymptomatic, adding to the difficulty of obtaining information from a family history that would accurately reflect the true clinical picture.⁸ In this study, we tested the utility of obtaining pedigree data from the proband, followed by application of a scoring system based on previous published stringent criteria.⁷ For our study, this practice led to the identification of a sizable cohort of patients whose family members are at risk of developing disease and who are recommended to undergo routine, repetitive screening for development of FDCM by established guidelines. In clinical practice obtaining such a 3 generation pedigree would be expected to consume about 10–20 minutes of a clinic visit and is achievable by physician extenders and/or support staff once adequately trained. Once FDCM is identified, referral to a cardiovascular genetics specialist or specialty clinic may be useful for investigation of a genetic diagnosis and family follow up.

Prevalence and prognosis

Systematic prospective family screening studies have identified familial disease in up to 50% of cases.^{1,2,9} Our study identifies a somewhat smaller proportion with definite or probable (26%) or possible (12.3%) FDCM. The combined total of 38.3% is less than

previously reported, however, we did not perform prospective clinical evaluation in family members. Therefore, although we detected almost ten-fold more FDCM than reported in the UNOS registry, had we looked prospectively, we may have identified even more individuals with FDCM. Finally, the familial nature of FDCM is supported in our cohort by identification of genetic diagnosis in 50% of a subset of confirmed and probable FDCM subjects, further substantiating pedigree-based diagnosis of FDCM in this cohort.

Due to the presumed chronic nature of biologic injury in FDCM, one might suspect that the transplant population would be enriched with FDCM patients. Supporting this, recently published data from the Netherlands¹⁰ suggests a worsened prognosis among stable heart failure patients with inherited disease. However, in that cohort there exists a highly penetrant founder mutation, potentially skewing the data. Our more heterogeneous study population does not appear to be enriched with FDCM patients, suggesting that perhaps FDCM is not more likely to progress to end stage heart failure than IDCM. This observation would be consistent with data published by investigators at the Mayo Clinic in stable heart failure patients, which indicated that prognosis was similar in patients with familial and idiopathic DCM.¹¹ Clearly, further studies in this area are needed to establish the impact of FDCM on prognosis in ESHF.

It is interesting to note that the diagnosis of FDCM is increasing over time in the UNOS registry. While this may be the product of increasing awareness of the familial nature of DCM amongst transplant cardiologists, even at its highest prevalence (5.3%) during the 2005–2010 era, our study indicates a substantial majority of FDCM continues to go undiagnosed at the time of transplant listing.

Clinical indicators of diagnosis

We sought to understand whether echocardiographic indices might be used to differentiate IDCM from FDCM among end stage heart failure patients. IDCM was associated with increased left atrial volume index & mitral regurgitation. Despite these findings, there were no significant differences in left ventricular end diastolic volume between FDCM and IDCM. These data do not strongly support the utility of echocardiographic features to identify FDCM. Further prospective studies would be helpful and could include a 3-dimensional evaluation of ventricular changes.

Study limitations

The retrospective nature of this study limited our ability to consecutively assess transplant patients for inherited cardiomyopathy. This may introduce survivor bias to some degree. As with all UNOS analyses, available data is limited and there is attrition with incomplete data and follow up in a small but measurable subset of patients in the dataset. However, there is an extended track record for using the UNOS dataset to draw inferences about survival relationships post transplant and our approach to data analysis using these data is in line with prior publications. Finally, we present analysis from a single center and there may be limitations in applying these findings to the entire UNOS cohort.

Conclusions

Despite decades of evidence supporting a genetic etiology of DCM (reviewed in^{12,13}), the adoption of guidelines to screen patients for FDCM by clinicians has been slow. In this transplant population, in which at least one or more cardiologists has presumably evaluated each individual, the diagnosis of FDCM is missed in a large majority of cases. We believe the data presented here should impact clinical practice among general cardiologists and heart failure specialists. Specifically, practice and guidelines should be updated to include obtaining a 3-generation pedigree, with appropriate scoring and clinical family screening, for all patients referred for advanced therapies.

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Figure 1.

Study flow diagram. *The UNOS diagnosis entered at the time of transplant listing, including DCM: idiopathic; DCM: myocarditis; DCM: other; DCM: post partum; DCM: familial; DCM: Adriamycin; DCM: viral; DCM: alcoholic. All other UNOS diagnoses were excluded, including ischemic cardiomyopathy, hypertrophic cardiomyopathy, restrictive myopathy, congenital heart disease, and valvular heart disease. Definition of confirmed FDCM, probable FDCM, or possible FDCM as previously defined (7). Briefly, confirmed FDCM is defined as cardiomyopathy confirmed by medical records obtained in 2 family members: the index patient and at least 1 other first-degree or second-degree family member. Probable FDCM is defined as cardiomyopathy confirmed by medical records in the index patient plus at least 1 first-degree or second-degree relative with compelling evidence of cardiomyopathy for which medical records were unavailable. Possible FDCM is defined as confirmed DCM in the index patient plus 1 of the following in at least 1 first-degree or second-degree relative: heart transplant because of non-ischemic cardiomyopathy, history of congestive heart failure because of non-ischemic cardiomyopathy, left ventricular dilation with normal systolic function and no evidence of other etiology, documented conduction system disease (electrocardiography or echocardiography), pacemaker, internal cardioverter-defibrillator, or history of sudden cardiac death without ischemic etiology. DCM, dilated cardiomyopathy; FDCM, familial dilated cardiomyopathy; OHT, orthotopic heart transplant; UNOS, United Network for Organ Sharing.

Figure 2.

Pre-pedigree diagnosis in 73 consecutive living adult patients with end-stage heart failure in the UNOS registry that received their care at the Yale Center for Advanced Heart Failure and diagnosis in those patients after a 3-generation pedigree analysis was performed.

Table 1

Clinical Characteristics of 16,091 Patients With DCM Identified in the UNOS Database

Recipient Characteristics	Overall DCM (<i>n</i> = 16,091)	FDCM (<i>n</i> = 492)	IDCM (<i>n</i> = 15,599)	<i>P</i> Value
Age, mean $\pm$ SD, y	48.3 $\pm$ 12.6	42.1 $\pm$ 13.1	48.5 $\pm$ 12.5	0.0001
Sex, No. of males (%)	11,059 (68.7%)	311 (63.2%)	10,748 (68.9%)	0.007
Race, No. white (%)	10,775 (67.0%)	359 (73.0%)	10,416 (66.8%)	0.017
Diabetes mellitus	2,113 (16.2%)	35 (7.8%)	2,078 (16.5%)	<0.0001
COPD	264 (2.7%)	5 (1.8%)	259 (2.7%)	0.36
History of Prior Cardiac Surgery	944 (5.9%)	33 (6.7%)	911 (5.8%)	0.42
BMI, mean $\pm$ SD, kg/m ²	26.0 $\pm$ 4.9	25.7 $\pm$ 4.9	26.0 $\pm$ 4.9	0.33
History of Smoking	4590 (30.1%)	145 (30.2%)	4445 (30.1%)	0.94
Dialysis	400 (2.6%)	7 (1.5%)	393 (2.7%)	0.11
Serum creatinine, mean $\pm$ SD, mg/dL	1.4 $\pm$ 1.2	1.2 $\pm$ 0.4	1.4 $\pm$ 1.2	0.0001
PRA 20%	6914 (45.3%)	298 (62.1%)	6616 (44.7%)	<0.0001

Table 2

Prevalence of FDCM and IDCM by Year of Diagnosis in the UNOS Database

	1990–1994	1995–1999	2000–2004	2005–2010	Total 1990–2010
Overall DCM (% total)	3652 (100%)	3703 (100%)	3375 (100%)	4542 (100%)	16,091 (100%)
IDCM (% total)	3596 (98.5%)	3623 (97.8%)	3270 (96.9%)	4303 (94.7%)	15,599 (96.9%)
FDCM (% total)	56 (1.5%)	80 (2.2%)	105 (3.1%)	239 (5.3%)	492 (3.1%)

Table 3

Relationship between UNOS Diagnosis, Post-Pedigree Diagnosis, Pedigree Findings that Support Post-Pedigree Diagnosis, and Genetic Testing Results

UNOS diagnosis	Post-pedigree classification	Pedigree findings	Genetics
DILATED MYOPATHY: IDIOPATHIC	Confirmed FDCM	brother with clinically confirmed DCM (tx)	
DILATED MYOPATHY: FAMILIAL	Confirmed FDCM	2 sons with clinically confirmed DCM, mother SCD, maternal cousin SCD, maternal cousin DCM, maternal uncle DCM, maternal grandmother DCM by report	Negative
DILATED MYOPATHY: IDIOPATHIC	Confirmed FDCM	brother with clinically confirmed DCM (tx)	
DILATED MYOPATHY: POST PARTUM	Confirmed FDCM	son with clinically confirmed DCM (tx)	Negative
DILATED MYOPATHY: FAMILIAL	Confirmed FDCM	father DCM (tx), paternal uncle HF death	LMNA
DILATED MYOPATHY: IDIOPATHIC	Confirmed FDCM	mother with clinically confirmed DCM (tx)	Negative
DILATED MYOPATHY: IDIOPATHIC	Confirmed FDCM	father with clinically confirmed DCM	Negative
DILATED MYOPATHY: POST PARTUM	Confirmed FDCM	sister with clinically confirmed DCM	EMD
DILATED MYOPATHY: OTHER SPECIFY	Confirmed FDCM	sister with clinically confirmed DCM	LMNA
DILATED MYOPATHY: IDIOPATHIC	Confirmed FDCM	niece PPM CM, daughter CM, paternal aunt DCM	
DILATED MYOPATHY: IDIOPATHIC	Probable FDCM	paternal uncle with clear DCM by report	
DILATED MYOPATHY: IDIOPATHIC	Probable FDCM	father with clear DCM by report	
DILATED MYOPATHY: OTHER	Probable FDCM	father CM, paternal grandmother and grandfather with clear DCM by report	
DILATED MYOPATHY: IDIOPATHIC	Probable FDCM	father, uncle, grandfather with clear systemic muscular disorder by report	
DILATED MYOPATHY: FAMILIAL	Probable FDCM	brother SCD, nephew with clear DCM and ICD by report	DSP
DILATED MYOPATHY: IDIOPATHIC	Probable FDCM	sister with clear DCM, LVAD, ICD by report	LMNA
DILATED MYOPATHY: IDIOPATHIC	Probable FDCM	father CM, 2 brothers with clear DCM, paternal grandmother clear DCM by report	VUS
DILATED MYOPATHY: IDIOPATHIC	Probable FDCM	maternal uncle clear DCM, maternal grandfather clear DCM by report	
DILATED MYOPATHY: IDIOPATHIC	Probable FDCM	sister clear DCM and SCD by report	

Data are presented so as to avoid potential patient identifiers. Tx, transplant; LMNA, Lamin; EMD, Emerin; DSP, Desmoplakin; VUS, Variant of unclear significance.

Table 4

Clinical and Echocardiographic Characteristics of Consecutive Living Adult Patients with End-Stage Heart Failure from the UNOS Registry that Received their Care at the Yale Center for Advanced Heart Failure with Diagnosis of IDCM or FDCM After 3-generation Pedigree Analysis

	Overall (n = 53)	IDCM (n = 39)	FDCM (n = 14)	P Value
Age, mean ± SD, y	46 ± 13	48 ± 13	43 ± 12	0.204
Sex, No. of males (%)	37 (69.8)	27 (69.2)	10 (71.4)	0.878
Race, No. white (%)	38 (71.7)	28 (71.8)	10 (71.4)	0.633
BMI, mean ± SD, kg/m ²	27.4 ± 4.6	27.3 ± 4.8	27.5 ± 4.3	0.650
Atrial Arrhythmias, No. (%)	19 (40%)	13 (37%)	6 (50%)	0.436
Ventricular arrhythmias, No. (%)	24 (51%)	16 (46%)	8 (67%)	0.207
Conduction Disease on EKG, No. (%)	29 (73%)	25 (76%)	4 (57%)	0.333
Skeletal Myopathy, No. (%)	2 (3%)	0 (0%)	2 (11%)	0.019
Aortic root, n, mean ± SD, cm	52, 2.9 ± 0.4	38, 2.9 ± 0.4	14, 2.9 ± 0.3	0.860
Right ventricular Fractional Area Shortening, n, mean ± SD	40, 24.4 ± 11.6	30, 22.6 ± 11.4	10, 29.7 ± 10.8	0.053
Right ventricular basal diameter, n, mean ± SD, cm	49, 4.6 ± 0.8	36, 4.6 ± 0.9	13, 4.8 ± 0.7	0.192
Right atrial end systolic area, n, mean ± SD, cm ²	49, 22.4 ± 9.0	37, 22.2 ± 9.1	12, 22.8 ± 8.9	0.789
Left ventricular ejection fraction (Simpson's), n, mean ± SD	42, 22.3 ± 9.2	31, 21.8 ± 10.3	11, 23.6 ± 5.4	0.350
Left ventricular end diastolic dimension, n, mean ± SD, cm	53, 6.8 ± 1.1	39, 6.9 ± 1.0	14, 6.7 ± 1.1	0.635
Left ventricular end systolic dimension, n, mean ± SD, cm	53, 6.1 ± 1.3	39, 6.2 ± 1.1	14, 5.9 ± 1.2	0.762
Left atrial volume, n, mean ± SD, mL	42, 113 ± 49	30, 124 ± 45	12, 85 ± 49	0.044
Left atrial volume index, n, mean ± SD, mL/m ²	41, 57 ± 24	29, 64 ± 21	12, 43 ± 24	0.008
Mitral regurgitation, n, mean ± SD, 0 (none), 1 (mild), 2 (moderate), 3 (severe)	51, 2.1 ± 0.8	37, 2.2 ± 0.8	14, 1.7 ± 0.8	0.045
Mitral valve annulus, parasternal long axis, n, mean ± SD, cm	51, 3.6 ± 0.7	37, 3.6 ± 0.6	14, 3.5 ± 0.9	0.816
Mitral valve annulus, 4 chamber view, n, mean ± SD, cm	48, 3.6 ± 0.7	35, 3.6 ± 0.7	13, 3.7 ± 0.8	0.880
Mitral valve annulus, 3 chamber view, n, mean ± SD, cm	42, 3.3 ± 0.6	32, 3.4 ± 0.5	10, 3.0 ± 0.8	0.097