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LV dysfunction

Progression of preclinical diastolic dysfunction to the development of symptoms

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ABSTRACT

Background Preclinical diastolic dysfunction (PDD) has been defined as subjects with normal systolic function, diastolic dysfunction but no symptoms of heart failure (HF). The clinical phenotype and natural history of the syndrome remains poorly defined. This study's objective was to determine the clinical phenotype and progression to HF in a group of patients with normal systolic function and moderate or severe diastolic dysfunction as determinate by Doppler criteria without any clinical diagnosis of HF according to the Framingham criteria or any symptoms of HF, specifically dyspnoea, oedema or fatigue at the time of echocardiography.

Methods The authors used resources of the Mayo Clinic echocardiography database to consecutively select among patients who had an echocardiogram in 2005, a cohort with moderate or severe diastolic dysfunction by Doppler criteria and EF ≥50%. Patients could not have a diagnosis of HF, or any HF symptoms—specifically dyspnoea, oedema or fatigue—at the time of echocardiography; nor grade 3 or greater valvular dysfunction (except tricuspid valve). A total of 82 patients had their medical chart reviewed. Primary endpoint was the time to the development of (1) HF according to the Framingham criteria or (2) any symptoms of dyspnoea, oedema or fatigue.

Results The mean age of the cohort of PDD subjects was 69±10 years with a female (67%) preponderance. Presence of hypertension was 76%, coronary artery disease was 29%, paroxysmal atrial fibrillation was 26%, estimated creatinine clearance <60 ml/min was 51%. The 2-year cumulative probability of development of HF according to the Framingham criteria was 1.9%; however, the 2-year cumulative probability of development of any symptoms was 31.1%. The 2-year cumulative probability for cardiac hospitalisation was 21.2%. Peripheral vascular disease and hypertension were independently associated with increased likelihood for the development of symptoms.

Conclusion The study demonstrates that hypertension, hyperlipidaemia, CAD and renal dysfunction are prevalent in patients with PDD. More importantly, although the progression to the development of clinical HF over 2 years was low, there was a moderate degree of progression to development of symptoms and cardiac hospitalisations over 2 years. Based on the finding that only PVD and hypertension were independently associated with the progression to the development of symptoms in subject with PDD, the authors speculate that ventricular-arterial interaction may be important to the progression of diastolic dysfunction to the development of symptoms.

INTRODUCTION

In the past decade, there has been significant progress in understanding diastolic heart failure or heart failure with preserved systolic function. Multiple studies have determined that diastolic heart failure is common and carries a very similar prognosis to heart failure with decreased systolic function.[1-6] A recent study by Achong et al reported in a cohort study that diastolic dysfunction determined by echocardiography Doppler assessment is associated with all-cause mortality and that the population whose diastolic function improved over time had a more favourable outcome.[7] In the AHA/ACC classification of heart failure (HF), stage B is defined as patients with abnormal heart structure/function without symptoms.[8] This concept of preclinical HF is based on the fact that abnormal heart structure/function can be detected by complementary methods before the development of symptoms. Patients with those abnormalities may progress to heart failure and are at increased risk of adverse cardiac events, including atrial fibrillation.[9] [10] The echocardiographic characterisation of diastolic dysfunction has also evolved[11] and echocardiographic analysis of diastolic dysfunction is reliable and is performed on a routine basis at most centres.[12]

Stage B or preclinical diastolic dysfunction (PDD), has been defined as subjects with normal systolic function, diastolic dysfunction but no symptoms of HF. Population-based studies have demonstrated that PDD is prevalent in the community.[3] Specifically, we have previously reported that in Olmsted County, Minnesota, 6.8% of the population above 45 years old and 16.5% of those above 65 years old with hypertension or coronary artery disease had moderate to severe PDD. Importantly, the subjects with PDD had a higher mortality compared to subjects with normal diastolic function.[3] Another population based study in Canberra, Australia, showed a prevalence of 4.9% in an elderly population (60–86 years old).[13] Despite the prevalence of PDD, the clinical phenotype and natural history of the syndrome remain poorly defined. There are limited data about the clinical characteristics of patients with PDD.

We aimed to determine the clinical phenotype and progression to the development of HF in a group of patients with normal LV ejection fraction and moderate or severe diastolic dysfunction as determinate by Doppler criteria without a clinical diagnosis of HF according to the Framingham criteria or any symptoms of HF, specifically dyspnoea, oedema or fatigue at the time of echocardiography. The primary endpoint was the time to the development of (1) HF according to the Framingham criteria or (2) any symptoms of dyspnoea, oedema or fatigue which had to be a chief complaint and not explained

by other medical condition. The secondary endpoint was cardiac hospitalisation. We also attempted to identify the clinical characteristics that could predict this progression to the development of symptoms or cardiac hospitalisation.

METHODS

The Mayo Clinic echocardiography database stores the echoes that are done in the Mayo Health system, approximately 30 000 a year. Using the Mayo Clinic echocardiography database, we consecutively selected 82 patients with moderate or severe diastolic dysfunction by Doppler criteria in 2005 and preserved EF. We excluded patients with a clinical diagnosis of HF according to the Framingham criteria or any symptoms of dyspnoea, oedema or fatigue; those with an EF less than 50%; grade 3 or greater valvular dysfunction (with the exception of tricuspid regurgitation) or atrial fibrillation at time of echocardiography. The study was approved by the institutional review board. Data collection was obtained through complete review of medical records until October 2007.

Echocardiography was performed according to guidelines of the American Society of Echocardiography[14] and diastolic function was classified integrating pulsed-wave Doppler examination of mitral inflow before and during Valsalva manoeuvre and of pulmonary venous inflow and Doppler tissue imaging of the mitral annulus.[3] In order to be classified with moderate or severe diastolic dysfunction, patients had to have evidence of elevated left ventricle filling pressure; that is E/e' greater than 10 with pseudo-normal filling or restrictive filling pattern of E and A waves as previously described and validated.[15]

Clinicians' diagnoses were used to identify all comorbidities. In addition, patients with three blood pressure measures greater than 140/90 mm Hg were considered hypertensive; those with low-density lipoprotein (LDL) greater than 140 mg/dl, high-density lipoprotein (HDL) less than 40 mg/dl or triglyceride (TG) greater than 150 mg/dl were classified as having hyperlipidaemia and patients with angiographic evidence of coronary artery disease (one or more vessel greater than 50% obstruction) or a positive stress test were considered as having coronary artery disease. Creatinine clearance (CrCl) was estimated using the Cockcroft-Gault formula.[16] The closest serum creatinine weight and height measure to the baseline echocardiogram were used for BMI and creatinine clearance calculation.

The beginning of follow-up was defined as first echocardiogram with ejection fraction greater than 50% and moderate or severe diastolic dysfunction. The primary endpoint was the time to the development of (1) HF according to the Framingham criteria or (2) any symptoms of dyspnoea, oedema or fatigue which had to be a chief complaint and not explained by other medical condition. The secondary endpoint was cardiac hospitalisation. Mean follow-up was 721 days. At the end of follow-up, all patients were alive as verified on our clinic records and by a public social security death index research tool.

Statistical analysis

Overall summaries were presented as means and standard deviations for continuous variables. Continuous variables were compared between groups using the Wilcoxon rank-sum tests. Categorical variables are summarised as percentages, and compared between groups using χ^2 tests. The cumulative probability of hospitalisation, symptoms, and atrial fibrillation were estimated using the Kaplan-Meier method. Potential risk factors for these endpoints were evaluated using Cox proportional hazards models. The multivariate models were selected using a stepwise selection technique. Only variables in the model that were less than 0.05 were included in the final model.

RESULTS

Clinical characteristics of the 82 patients are reported in table 1. Mean age was 69 (minimum 35, maximum 86, SD 10.65), with a female preponderance 67%. Cardiovascular diseases were prevalent, hypertension 76%, coronary artery disease 29%, paroxysmal atrial fibrillation 26%, history of myocardial infarction 16% and peripheral vascular disease (PVD) 12%.

Among patients with hypertension, blood pressure was consistently less than 140/90 mm Hg in only 32%. Cardiovascular disease risk factors were also highly prevalent, hyperlipidaemia 57%, estimated CrCl <60 ml/min 51%, BMI >30 33%, diabetes mellitus 12%.

Echocardiograms were obtained for a variety of reasons: 29% due presence or concerns for rhythm disorders, 26% due to presence or concerns for valvular disorders, 20% due to concerns of CAD, 12% for screening and 13% for miscellaneous reasons. All patients were in sinus rhythm at time of echocardiogram. Echocardiogram data are shown in table 1. The mean ejection fraction was 65.5% (SD 6.14). Left ventricular hypertrophy was

Table 1 Baseline clinical and echocardiography data

Variable	No	%
Age (years)	82 (mean age 69)	
Female gender	55	67
Cardiovascular disease risk factors		
Hyperlipidaemia	46	57
Smoke history	37	45
BMI >30	26	33
Obstructive sleep apnoea	8	10
Diabetes mellitus	10	12
Estimated CrCl <60 ml/min	40	51
Estimated CrCl <40 ml/min	9	11
Cardiovascular comorbidities		
Hypertension	62	76
Coronary artery disease	24	29
History of MI	13	16
Paroxysmal atrial fibrillation	21	26
Moderate aortic or mitral valve dysfunction	15	18
Peripheral vascular disease	10	12
Pacemaker	5	6
Echocardiography data		
RWMA	9	11
LVH	8	10
	Mean	**SD**
Ejection fraction %	65.46	6.14
Mitral inflow E velocity m/s	0.91	0.24
Mitral inflow A velocity m/s	0.75	0.26
E/A	1.30	0.52
Deceleration time milliseconds	195.58	46.54
A duration milliseconds	134.66	15.92
Tissue Doppler e m/s	0.06	0.01
E/e	14.77	5.62
RVSP mm Hg	35.40	10.67
Left atrium volume index ml/m²	40.56	9.86

A, atrial component of mitral filling; BMI, body mass index; CrCl, creatinine clearance; E, early component of mitral filling; E/A, the ratio of the mitral early (E) and atrial (A) components of the mitral inflow velocity profile; E/e, early diastolic mitral inflow velocity/ early diastolic mitral annular velocity; LVH, Left ventricular hypertrophy; MI, myocardial infarction; RVSP, Right ventricle systolic pressure; RWMA, regional wall motion abnormalities.

present only in 10% of the patients and RWMA in 11%. Right ventricle size and function were normal in the majority of the patients (92% and 95%, respectively). Indeed, patients had significant diastolic dysfunction as evident by a mean E/e' of 14.77 and mean LA volume index of 41 ml/m^2.

We also obtained data regarding medications. Fifty-nine per cent were on β-blockers at the time of echocardiogram, while 56% were on aspirin, 41% on statins, 34% on diuretics, 28% on angiotensin converting enzyme inhibitors, 12% on angiotensin-receptor blocker, 12% on calcium channel blocker and 6% on digoxin.

Patients were followed up for a mean of 721 days for the development of HF according to the Framingham criteria or any symptoms of dyspnoea, oedema or fatigue. Once again, these symptoms had to be the chief complaint and other medical conditions were ruled out. Mean time for the development of symptoms was 529 days (SD 267).

The 2-year cumulative probability for development of HF according to the Framingham criteria was 1.9% (95% CI 0% to 5.4%). The 2-year cumulative probability for development of any symptoms of dyspnoea, oedema or fatigue was 31.1% (figure 1). The 2-year cumulative probability for development of either dyspnoea or oedema alone was 17.0% (95% CI 6.3% to 26.4%) and 5.6% (95% CI 0.0% to 11.7%) for the development of more than one symptom. A univariate analysis was performed for the development of symptoms; PVD, hypertension, right bundle branch block, moderate aortic or mitral regurgitation as well as diuretic use were statistically significant related to the development of symptoms. In a multivariate model, PVD and hypertension were independently associated with development of symptoms (HR: 6.91 and 11.15, respectively) (table 2). Of the patients who developed symptoms, 60% had a repeat echocardiogram on presentations of symptoms. The left ejection fraction (LVEF), diastolic function grade and LV mass did not change significantly from their baseline echocardiogram. Among patients who developed at least one symptom, a potential trigger for the development of the symptoms could be identified only in 52.2%. In 17.4% of patients, symptoms were precipitated by ischaemia, in another 17.4% by atrial fibrillation, in 8.7% by an increase in blood pressure and in 8.7% by a hospitalisation for other medical reasons. Importantly, in half of the PDD patients who developed symptoms, no precipitating factor could be identified. Of the patients who developed symptoms during the follow-up period, we obtained data regarding the change in
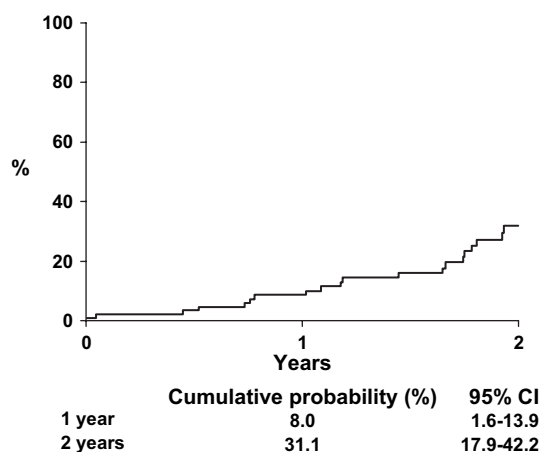
Table 2 Multivariate analysis

Multivariate analysis	HR	95% CI	p Value
Development of symptoms			
Hypertension	11.15	1.46 to 84.71	0.02
Peripheral vascular disease	6.91	2.51 to 18.99	<0.001
Cardiac hospitalisations			
Peripheral vascular disease	5.61	1.83-17.19	0.002

medications: 70% had no change in medications; 10% had angiotensin converting enzyme inhibitor added; 5% had angiotensin receptor blocker added; 5% had calcium channel blocker added; 5% had β-blocker added and 5% had β-blocker and diuretic added.

The 2-year cumulative probability for cardiac hospitalisation was 21.1% (95% CI 9.8% to 31.1%) (Kaplan-Meyer curve on figure 2). The mean time to hospitalisation was 388 days (SD 269). Forty per cent of those hospitalisations were related to rhythm disorders, with 80% atrial fibrillation, which highlights the elevated incidence of atrial fibrillation in this population with a mean left atrium volume index of 41 ml/m^2. Thirty-three per cent of hospitalisations were for cardiovascular surgery (50% CABG), 13% due to coronary artery disease, 6.5% for HF and 6.5% for hypertension emergency. In a univariate analysis, PVD, obstructive sleep apnoea and presence of pacemaker were statistically significantly related to cardiac hospitalisations. However, in our multivariate model only PVD was statistically significant (HR: 5.61, 95% CI 1.8 to 17.2, p=0.001) (table 2).

Paroxysmal atrial fibrillation was present in 26% of the patients at the beginning of follow-up. Among the 61 patients without a history of paroxysmal atrial fibrillation at baseline, the 2-year cumulative probability of new onset atrial fibrillation was 12.5% (95% CI 2.4% to 21.6%).

DISCUSSION

The current study is consistent with previous studies demonstrating that subjects with PDD are elderly with a female preponderance and high prevalence of cardiovascular comorbidities or risk factors. However, it extends previous studies and showed that although the progression to the development of clinical HF over 2 years is low, there was a moderate rate of progression to the development of symptoms.
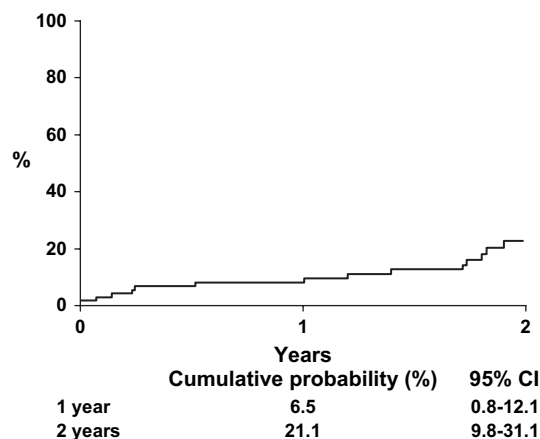

	Cumulative probability (%)	95% CI
1 year	8.0	1.6-13.9
2 years	31.1	17.9-42.2

Figure 1 Cumulative probability of development of symptoms by Kaplan-Meyer.

	Cumulative probability (%)	95% CI
1 year	6.5	0.8-12.1
2 years	21.1	9.8-31.1

Figure 2 Cumulative probability of cardiac hospitalisation by Kaplan-Meyer.

In patients with diastolic heart failure or heart failure with preserved ejection fraction, there is currently no specific therapy proved to decrease mortality. The fact that drugs that significantly change the prognosis of systolic heart failure are not effective in diastolic heart failure highlights the need for a better understanding of the pathophysiology of diastolic dysfunction. Particularly important is to understand the mechanisms behind the progression from asymptomatic to symptomatic diastolic dysfunction. Hence, the AHA/ACC classification of heart failure (HF) included stage B HF, which is defined as patients with abnormal heart structure/function without symptoms.[8] Lam and others[17] had attempted to answer some of those issues by comparing echocardiographic variables between patients with symptomatic stage C heart failure with preserved EF and patients with hypertension but no clinical heart failure. In their study, patients with heart failure had more impaired relaxation and increased diastolic stiffness compared with subjects with hypertension. Kawaguchi et al, by invasive haemodynamic studies in subjects with stage C diastolic heart failure, found not only higher left ventricle stiffness, but also higher arterial stiffness in patients with diastolic heart failure compared to individuals with hypertension.[18] A recent population-based study of patients with stage C diastolic heart failure showed that pulmonary hypertension was present in 83% of patients; importantly, the degree of pulmonary hypertension could not be fully explained only by increase in pulmonary venous hypertension, but there was also increase in pulmonary arterial hypertension.[19] It is also interesting to note that several studies report a high prevalence of renal insufficiency in patients with diastolic heart failure, suggesting that perhaps volume expansion plays a significant part in the pathophysiology of this disease. Indeed, in the current study, 50% of patients with PDD had renal insufficiency that was defined by calculated creation clearance of <60 ml/min. Therefore, proposed mechanisms for the progression of diastolic dysfunction include not only left ventricle stiffness, but also vascular stiffening (systemic and pulmonary) and volume expansion. We report for the first time that in patients with PDD (stage B HF), there was a moderate rate of progression to the development of symptoms in 2 years. Based on our finding that only PVD and hypertension were independently associated with the progression to the development of symptoms in subjects with PDD, we speculate that ventricular-arterial interaction may be important in the progression to the development of symptoms. It is certainly possible that PVD and hypertension were merely markers of cardiovascular disease and the cause—effect relation will require further investigation.

The substrate and, therefore, potential for the development of symptoms is certainly present in patients with PDD or stage B diastolic heart failure. Our study provides some insight in potential triggers for the development of symptoms. Among patients that developed at least one symptom, a potential trigger could be identified in 52.2%. In 17.4% of patients, symptoms were precipitated by ischaemia, in another 17.4% by atrial fibrillation, in 8.7% by an increase in blood pressure and in 8.7% by hospitalisation for other medical reasons. These findings are similar to our previous report of the precipitating factors for the development of decompensated (stage C/D) diastolic heart failure.[1] However, in our current study, approximately 50% of patients with PDD that developed symptoms did not have an apparent trigger suggesting that it may be due to progression of the diastolic dysfunction. Of the patients who developed symptoms, 60% had a repeat echocardiogram on presentations of symptoms. The left ejection fraction (LVEF), diastolic function grade and LV mass did not change significantly from their baseline echo. Hence, these observations would suggest that in this cohort of patients with preclinical diastolic dysfunction, the progression to the development of symptoms is multifactorial.

Atrial fibrillation was particularly common in our cohort. Diastolic dysfunction is known to be associated with LA enlargement and thus increases the risk of atrial fibrillation. Atrial fibrillation is likely to be poorly tolerated in subjects with PDD as the loss of atrial contraction and the decrease in diastolic filling time will result in increased LV end-diastolic pressure. In our study, atrial fibrillation was responsible for 40% of cardiac hospitalisations and may have predisposed to symptoms in 8.7% of patients.

LIMITATIONS

Our study does have limitations; it is a retrospective study in an enriched population referred to echocardiography and we do not have a control group without diastolic dysfunction. It is possible that, owing to limited sample size and short follow-up period, we do not have enough power to detect some associations. Moreover, the very similar echocardiography grade of diastolic dysfunction impaired analysis of echocardiography data as predictors of the development of symptoms or cardiac hospitalisations. We strive to compensate for those deficiencies with very accurate clinical information, collected by meticulous chart review and excellent echocardiography data. In addition, patients with questionable symptoms at baseline or any indeterminate echocardiography data were excluded.

CONCLUSION

In a population referred for echocardiography at a tertiary institution for a variety of reasons, patients with PPD were elderly with a female preponderance. Cardiovascular disease risk factors were very prevalent. There was a low rate to the progression of clinical HF in 2 years; however, there was a moderate rate of progression to the development of symptoms in 2 years as well as cumulative probability for cardiac hospitalisation. PVD and hypertension were independently associated with the development of symptoms. Our finding that only PVD and hypertension were independently associated with the progression to the development of symptoms in subject with PDD suggests that a ventricular—arterial interaction may be an important in the progression to the development of symptoms and deserves further investigation.

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