Right Ventricular Involvement in Fabry Disease

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The aim of the study was to describe right ventricular (RV) structural and functional changes in Fabry disease (FD). A detailed echocardiographic examination was performed in 58 patients with proven FD (mean age 40 ±16 years, 24 men). RV hypertrophy (RVH) was present in 40% of affected subjects with similar prevalence in both genders. Approximately two thirds of patients with left ventricular hypertrophy (LVH) also exhibited RVH. RV dilatation was not present in any subject. RV systolic dysfunction was noted in only 1 female subject. RV diastolic dysfunction was present in 47% of 45 subjects in whom RV filling was assessed. RV diastolic dysfunction was associated with the presence of RVH. A significant correlation between RV wall thickness and age ($r = 0.52$, $P < .001$) and left ventricular mass index ($r = 0.70$, $P < .001$) was noted. RVH with normal chamber size and preserved systolic but impaired diastolic function represents a typical RV structural change in FD. Its prevalence and degree are related to the prevalence and degree of LVH and the age of the patient. (J Am Soc Echocardiogr 2008;21:1265-1268.)

Keywords: Cardiomyopathy, Echocardiography, Fabry disease, Right ventricle

Fabry disease (FD) is an X-linked genetic disorder of glycosphingolipid metabolism caused by deficient activity of lysosomal enzyme α-galactosidase A. The disease is characterized by progressive intracellular accumulation of neutral glycosphingolipids, mainly globotriaosylceramide, in different tissues throughout the body, including the heart.[1] Left ventricular hypertrophy (LVH) is the hallmark of cardiac involvement in FD.[2] LVH is mostly concentric, and its development is progressive, occurring earlier in hemizygous men than in heterozygous women.[3-5] Left ventricular (LV) systolic function as expressed by conventional measures is mostly preserved in FD; however, diastolic function is usually mildly to moderately impaired. Nevertheless, restrictive pathophysiology with highly elevated resting LV filling pressures is rare.[6,7] Because the deposition of globotriaosylceramide may be found in all cardiac tissues, right ventricular (RV) involvement might be an anticipated phenomenon in FD. However, few data regarding this issue can be found in the current literature.[8] Therefore, the aim of our study was to characterize RV morphologic and functional changes in a series of patients with FD by using transthoracic echocardiography.

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MATERIALS AND METHODS

Study Population

Of the cohort of 102 subjects with genetically proven FD followed at our institution (Charles University of Prague, 1st Medical Faculty, 2nd Medical Department-Clinical Department of Cardiology and Angiology, General University Hospital), we retrospectively analyzed data of 58 patients (40 ± 16 years, 25 men) in whom listed exclusion criteria were absent. Exclusion criteria included inadequate image quality, previous or current enzyme replacement therapy, other than sinus rhythm (including previous pacemaker implantation for any reason), and the presence of congenital heart disease or significant valvulopathy. Study approval was granted by the institutional review board, and all patients gave signed informed consent. Detailed echocardiographic examination was performed in all patients. Blood pressure and heart rate were measured at the time of echocardiography.

Echocardiography

M-mode echocardiographic measurements of the left atrial, RV and LV end-diastolic diameters, and interventricular septal (IVS) and LV posterior wall thickness were performed in the parasternal long-axis view according to the recommendations of the American Society of Echocardiography.[9] RV dilatation was defined as RV end-diastolic diameter > 31 mm. LV end-diastolic volume, end-systolic volume, and ejection fraction were measured in the apical 4-chamber view using the modified Simpson's method.[10] LV mass was calculated by the method described by Devereux et al[11] and then indexed by height ^{2,7} ($LVMI^{-2.7}$). LVH was considered to be present if $LVMI^{-2.7}$ was more than 50 $g/m^{-2.7}$ in men and 47 $g/m^{-2.7}$ in women.[12]

Pulsed-wave Doppler recordings of mitral inflow and pulmonary venous flow velocities together with pulsed-wave tissue Doppler analysis of mitral annular diastolic velocities were obtained according to recently published recommendations.[13] On the basis of these measurements, LV filling pattern type was classified as normal, impaired relaxation, pseudonormal, or restrictive.[13]

The tricuspid annular plane systolic excursion (TAPSE) as an index of RV systolic function was measured on the 2-dimensional–guided

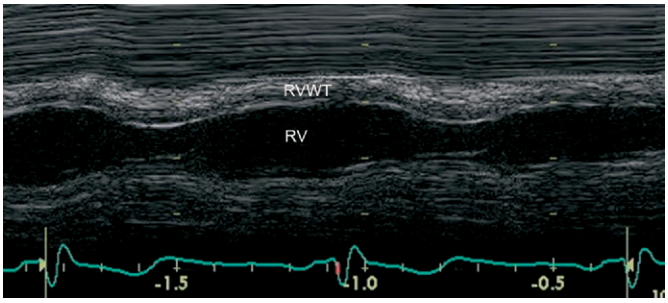

Figure 1 RVWT. Representative example of M-mode recording of RVWT from the subcostal long-axis view. *RV*, Right ventricular; *RVWT*, right ventricular wall thickness. Color figure online.

M-mode tracing using the apical 4-chamber view. RV systolic dysfunction was considered for TAPSE < 19 mm.[14] RV wall thickness (RVWT) was measured by M-mode at end-diastole from the subcostal long-axis view (Figure 1).[15] RV hypertrophy (RVH) was defined as an RVWT > 5 mm.[16]

Right atrial (RA) diameter was measured in mid-diastole using the apical 4-chamber view. RA dilatation was considered when the RA diameter exceeded 37 mm.[17]

To assess RV diastolic function, pulsed Doppler recordings of tricuspid inflow peak early (E) and late (A) velocities in apical 4-chamber view were obtained.[8,18] Normal RV diastolic function was considered when the E/A ratio was > 1, E-wave deceleration time (DT-E) was 150 to 220 ms, and normal RA size was present. Impaired relaxation filling pattern reflecting mild RV diastolic dysfunction was defined as an E/A ratio < 1 and a DT-E > 220 ms regardless of RA size. Pseudonormal filling pattern was considered if the E/A ratio was 1 to 2 with DT-E 150 to 220 ms and restrictive filling pattern if the E/A ratio was > 2 with DT-E < 150 ms, both in the presence of RA dilatation. These 2 patterns represented moderate and severe RV diastolic dysfunction. Peak transtricuspid pressure gradient was measured using continuous-wave Doppler in parasternal or apical views to obtain the greatest maximal velocity of tricuspid regurgitant signal. Pulmonary artery systolic pressure was calculated by adding an RA pressure estimate to the systolic transtricuspid pressure gradient.[19] RA pressure was estimated using the caval respiratory index based on the measurements of respiratory variations of the inferior vena cava in subcostal view.[20] Pulmonary hypertension was defined as a pulmonary artery systolic pressure of 40 mm Hg or greater.

All echocardiographic data were analyzed by a single observer (T.P.) and averaged over 3 heart beats recorded during quiet respiration, except for measurements of the inferior vena cava performed during normal respiration.

Statistical Analysis

Statistical analysis was performed with commercially available JMP 6.1.3. statistical software (SAS Institute Inc., Cary, NC). Data are expressed as mean ± standard deviation or as a number and percentage of subjects. Linear regression analysis was performed to assess the relationship between echocardiographic variables and age. A value of $P \leq .05$ was considered statistically significant.

RESULTS

Clinical and basic hemodynamic characteristics of the study patients are listed in Table 1. Women were significantly older than men. There were no differences regarding the heart rate or blood pressure measurements. Both genders were similarly affected by arterial hypertension. Renal insufficiency was more frequent in male hemizygotes. The prevalence of diabetes mellitus and coronary artery disease was higher in women.

Table 1 Clinical and basic hemodynamic characteristics

Variable	Men (n = 25)	Women (n = 33)
Age (y)	35 ± 12	44 ± 18*
Heart rate (bpm)	66 ± 11	69 ± 12
Systolic blood pressure (mm Hg)	126 ± 12	126 ± 20
Diastolic blood pressure (mm Hg)	74 ± 10	71 ± 11
Arterial hypertension (%)	8 (32%)	10 (30%)
Diabetes mellitus (%)	0 (0%)	6 (18%)
Coronary artery disease (%)	2 (8%)	6 (18%)
Renal insufficiency (%)	10 (40%)	5 (15%)
ACEI therapy (%)	8 (32%)	10 (30%)
Calcium antagonist therapy (%)	5 (20%)	8 (24%)
β-blocker therapy (%)	6 (24%)	10 (30%)

ACEI, Angiotensin-converting enzyme inhibitor.
Data are expressed as mean ± standard deviation or as a number and percentage of subjects.
*$P \leq .05$.

Table 2 Echocardiographic variables

Variable	Men (n = 25)	Women (n = 33)
IVS (mm)	14 ± 5	11 ± 3†
PWT (mm)	13 ± 4	10 ± 3‡
LVEDD (mm)	51 ± 5	47 ± 5‡
$LVMI^{-2.7}$ ($g/m^{-2.7}$)	68 ± 35	48 ± 21†
LVH (n, %)	18 (72)	13 (39)
LVEF (%)	65 ± 6	69 ± 5*
Left atrial diameter (mm)	40 ± 6	39 ± 7
RVEDD (mm)	24 ± 5	23 ± 5
RVWT (mm)	6 ± 2	5 ± 2*
RVH (n, %)	13 (52)	10 (30)
TAPSE (mm)	24 ± 4	24 ± 3
RA diameter (mm)	39 ± 4	37 ± 5*

IVS, Interventricular septal; *LVEDD*, left ventricular end-diastolic diameter; *LVEDV*, left ventricular end-diastolic volume; *LVEF*, left ventricular ejection fraction; *LVESD*, left ventricular end-systolic diameter; *LVESV*, left ventricular end-systolic volume; *LVH*, left ventricular hypertrophy; *LVMI*, left ventricular mass index; *PWT*, posterior wall thickness; *RVEDD*, right ventricular end-diastolic diameter; *RVWT*, right ventricular wall thickness; *RVH*, right ventricular hypertrophy; *TAPSE*, tricuspid annular plane systolic excursion; *RA*, right atrial.
Data are expressed as mean ± standard deviation.
*$P \leq .05$.
†$P \leq .01$.
‡$P \leq .001$.

Echocardiographic variables are listed in Table 2. IVS and posterior wall thickness, and LV end-diastolic diameter were significantly higher in men. Accordingly, $LVMI^{-2.7}$ was also significantly higher in male patients. LVH was noted in 31 patients (53%), more often in men (n = 18) than in women (n = 13). LV systolic function expressed as LV ejection fraction was preserved in all patients and slightly, but significantly, higher in women. With regard to LV diastolic function, a normal LV filling pattern was observed in 35 subjects (60%), impaired relaxation was observed in 13 patients (23%), and pseudonormal LV filling was observed in 10 patients (17%). Restric-