Do women have impaired regional systolic function in hypertensive heart disease? A 3-dimensional echocardiography study

Jürgen Frielingsdorf a,*, Michele Genoni a, Otto M. Hess b, Frank A. Flachskampf c

a Heart Center, City Hospital Triemli, Birmensdorferstrasse 497, 8063 Zürich, Switzerland
b Cardiology, University Hospital, Bern, Switzerland
c Medical Clinic II, University Hospital, Erlangen, Germany

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Wall thickness;
Three-dimensional echocardiography

Abstract
Aims: In pressure overload left ventricular (LV) hypertrophy, gender-related differences in global LV systolic function have been previously reported. The goal of this study was to determine regional systolic function of the left ventricle in male and female patients with hypertensive heart disease.

Methods and results: Regional LV function was analyzed from multiplane transesophageal echocardiography with three-dimensional (3D) reconstruction of the left ventricle. In 24 patients (13 males and 11 females), four parallel (2 basal and 2 apical) equidistant short axis cross-sections from base to apex were obtained from the reconstructed LV. In each short axis 24 wall-thickness measurements were carried out at 15° intervals at end-diastole and end-systole. Thus, a total of 192 measurements were obtained in each patient. Wall thickening was calculated as difference of end-diastolic and end-systolic wall thickness, and fractional thickening as thickening divided by end-diastolic thickness.

Fractional thickening and wall stress were inversely related to end-diastolic wall thickness in both, males and females. Females showed less LV systolic function when compared to males (p < 0.001). However, when corrected for wall stress, which was higher in females, there was no gender difference in systolic function.

Conclusion: There are regional differences in LV systolic function in females and males which are directly related to differences in wall stress. Thus, gender-related differences in LV regional function are load-dependent and not due to structural differences.

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* Corresponding author. Tel.: +41 1 466 1313; fax: +41 1 466 2599.
E-mail address: juergen.frielingsdorf@triemli.stzh.ch (J. Frielingsdorf).

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Introduction

Gender differences in left ventricular (LV) systolic function have been documented in patients with aortic stenosis and hypertensive heart disease. In most studies, global LV systolic function (e.g. ejection fraction, fractional shortening, cardiac index) was determined to define these differences. However, gender differences in regional LV systolic function (e.g. myocardial thickening) have not been studied extensively. Females with hypertrophic obstructive cardiomyopathy showed better regional systolic function, but this difference was mainly related to regional wall thickness and wall stress and not to true structural changes.

Regional systolic function is, among many parameters, dependent on myocardial wall thickness and wall stress. An inverse relationship between end-diastolic wall thickness and regional systolic function has been described. Furthermore, wall stress has been shown to be an important determinant of systolic function. Regional differences in wall thickness and wall stress may result in regional heterogeneity of systolic function.

Since there are no data on regional systolic function in males and females with hypertensive heart disease, the present study aimed to analyze these patients by using three-dimensional (3D) transesophageal echocardiography. Systolic function was related to wall thickness and wall stress, respectively, to correct for gender differences in these patients.

Methods

Study population

In the present analysis 24 patients (13 males and 11 females) with hypertensive heart disease were studied. At the time of examination all subjects were in sinus rhythm with similar heart rates in males and females (69 ± 10, 71 ± 11 bpm, respectively; no significant difference). Negative inotropic agents were evenly distributed (Table 1). LV ejection fraction was calculated according to Simpson’s rule, using the end-diastolic and end-systolic cavity volumes in two apical 2D echocardiographic views (2-chamber and 4-chamber).

Patients with hypertensive heart disease were selected on the basis of a history of high blood pressure (diastolic values above 90 mmHg and/or systolic values above 140 mmHg). LV hypertrophy was considered present when LV mass index was >116 g/m² in men and >104 g/m² in women. No patient with hypertensive heart disease showed signs of LV outflow tract obstruction or abnormal motion of the mitral valve. Obesity was common and more pronounced in women. Patients were excluded when there was either echocardiographic evidence of segmental wall motion abnormalities, impaired LV function, significant valvular heart disease or clinical evidence of coronary artery disease, bundle branch block or atrial fibrillation. Informed written consent was obtained from each patient and the regional ethics committee approved the study.

Data acquisition and 3D reconstruction

This method has been described previously by our group. In brief, after each patient gave written informed consent, a multiplane transesophageal echocardiographic study was performed under mild sedation (2.5–5 mg of midazolam intravenously). Acquisition of data for quantitative 3D reconstruction was performed with a modified multiplane transesophageal transducer (5 MHz, 64 elements, phased array; Hewlett-Packard) using the long axis view of the LV from the mid esophagus. The transducer was connected to a Sonos 2500 echo machine (Hewlett-Packard). The modification of the commercially available probe refers to an externally mounted stepper motor which enables a stepwise rotation of the scanning plane in 2° increments from 0° through 180°. The imaging system was connected to an external data-acquisition and processing system (Echoscan, TomTec Imaging Systems GmbH, Munich, Germany) which controls image acquisition and mechanical rotation of the imaging plane based on ECG and respiration gating. After complete image acquisition, raw data were processed to produce a 3D reconstruction.

Table 1 Patient characteristics, medications and 2D echocardiographic data in males and females

<table>
<thead>
<tr>
<th></th>
<th>Males (n = 13)</th>
<th>Females (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 ± 13</td>
<td>64 ± 14</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 4</td>
<td>29 ± 3*</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>9/13 (69%)</td>
<td>7/11 (64%)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>1/13 (8%)</td>
<td>1/11 (9%)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>63 ± 8</td>
<td>66 ± 10</td>
</tr>
<tr>
<td>Septum (mm)</td>
<td>14 ± 3</td>
<td>14 ± 4</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
<td>12 ± 3</td>
<td>13 ± 4</td>
</tr>
<tr>
<td>ED diameter (mm)</td>
<td>53 ± 5</td>
<td>49 ± 10*</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>172 ± 32</td>
<td>162 ± 37</td>
</tr>
</tbody>
</table>

BMI, body mass index; ED, end-diastolic; LV, left ventricular. *p < 0.05.
of the analyzed structure resulting in a cone-shaped voxel volume. This 3D data set was used to reconstruct a tissue gray value display of any desired cross-section through the heart closely resembling conventional echocardiographic images in cine loop format at 25 frames/s.

Data analysis

The true long axis of the 3D reconstructed left ventricle was defined as a line through the apex and the mitral annulus determining the center point of the annulus in the long-axis view and, for optimal orientation of the axis, in a simultaneously displayed short-axis view at the mitral annulus. In each subject four parallel equidistant short axis cross-sections from the base to the apex were obtained from the reconstructed LV (Fig. 1). In each of the FOUR slices (basal, mediobasal, medi-oapical, and apical), epicardial and endocardial boundaries were traced manually at end-diastole and end-systole. Twenty-four wall thickness (h) measurements were carried out at 15° intervals at end-systole and end-diastole (192 measurements in each patient). Papillary muscles were excluded from wall-thickness measurements where they could be separated from the LV wall.

Wall thickening (ΔT, mm), a parameter of regional systolic function, was calculated as difference between end-systolic (ES) and end-diastolic (ED) wall thickness (ΔT = hES - hED), and fractional thickening (fT) as thickening divided by end-diastolic thickness (fT = ΔT/hED). Meridional wall stress (MWS) was approximated as MWS = Pr/2h(1 + h/2r), where MWS = meridional wall stress in kdynes/cm², P = systolic ventricular pressure, r = internal radius of the ventricle, and h = left ventricular wall thickness. The measurement of the radius was performed for each wall-thickness measurement to exactly calculate wall stress for each wall segment. Systolic LV pressure was approximated by measuring systemic blood pressure using cuff manometry at the time of transesophageal echocardiography.

Statistical analysis

Between-group comparisons with regard to differences in fractional thickening and wall stress were performed by a one-way analysis of variance (ANOVA) for continuous variables followed by the Scheffe’s procedure if the p value was significant (p < 0.05). A simple linear regression was used to determine the relation between fractional thickening and wall stress.

Results

Fractional wall thickening and wall stress

When all regional values of fractional thickening (n = 2304) were plotted against end-diastolic thickness (Fig. 2), a clear inverse relation was observed in each group: the thicker the LV wall at end-diastole,
the lesser fractional thickening ($p < 0.001$ for trend). This relation was reflected in the hypertrophied as well as non-hypertrophied muscle in all subjects. Compared to males, females showed less fractional thickening for matched end-diastolic wall thickness ($p < 0.001$ for trend).

A similar inverse relation was observed when all regional values of wall stress ($n = 2304$) were plotted against end-diastolic thickness (Fig. 3): the thicker the LV wall at end-diastole, the lower wall stress ($p < 0.001$). Again, this relation was reflected in the hypertrophied as well as non-hypertrophied muscle in all subjects. Compared to males, females showed higher wall stress for matched end-diastolic wall thickness ($p < 0.001$).

Discussion

In the animal model of pressure overload, female rats demonstrated better LV contractile reserve than male rats despite a similar degree of LV hypertrophy and wall stress. Striking gender-related differences in the expression of key genes that are known to play critical roles in cardiac calcium regulation and contraction resulted in better systolic function of female rats, and with the same extent of LV hypertrophy male but not female rats showed an early transition to heart failure. In mice, estradiol was a mediator of atrial natriuretic factor which counterbalanced myocyte hypertrophy. However, these relations have not been analyzed in human studies. In the present study on patients with hypertensive heart disease 3D reconstruction of the heart allowed to measure directly wall thickness, contractile function from systolic wall thickening, and meridional wall stress in any region of the left ventricle. In contrast to the animal studies, females showed less LV systolic function when compared to males. However, when corrected for wall stress, which was higher in females, there was no gender difference in systolic function.

Clinical studies have documented gender differences in LV systolic function in response to increased afterload such as occurs in aortic stenosis or in hypertensive heart disease. Cardiac performance was more frequently preserved in female compared with male patients. Carroll et al. showed that despite a similar degree of aortic stenosis and afterload, the left ventricle of women had a greater fractional shortening and maximum positive dP/dt when compared to men. However, these gender differences were directly
related to differences in wall stress that derived from distinctive patterns of geometric adaptation of the LV to aortic stenosis. Thus, regional differences in wall stress\textsuperscript{8,9} may result in regional heterogeneity of systolic function.\textsuperscript{7,10} In fact, women had less chamber dilation and higher relative wall thickness, resulting in less wall stress, when compared to men.\textsuperscript{19}

In a subgroup of the Framingham Heart Study women with isolated systolic hypertension had increased wall thickness and mass without LV chamber enlargement, while men had LV dilation and increased LV mass without increased wall thickness.\textsuperscript{22} Thus, the geometric pattern of increased LV mass differed by gender. Similar to these results Aurigemma et al.\textsuperscript{2} concluded that better fractional shortening and high ejection fraction in elderly women with aortic stenosis were the consequence of alterations in LV geometry and wall stress and not of changes in myocardial contractile function. The overall stress-shortening relations were equal in men and women,\textsuperscript{2} which has also been shown in our patients with hypertensive heart disease. However, up to now the evaluation of gender differences in systolic function has been based on measuring global stress-shortening relations\textsuperscript{2,19} without considering the impact of regional variation in wall thickness and wall stress on systolic function. Furthermore, there are no data on regional systolic function in males and females with hypertensive heart disease. In the present analysis 3D transesophageal echocardiography allowed to determine contractile function from systolic wall thickening in relation to different degrees of wall thickness, and wall stress in any region of the left ventricle independent on the geometric LV pattern.

Myocardial wall thickness may further influence systolic LV function. An inverse relationship between wall thickness and regional systolic function has been described,\textsuperscript{4-7} which is reflected in the present study. This relationship exists partly by definition since fractional thickening is calculated as thickening divided by end-diastolic thickness. For similar reasons there is an inverse relationship between wall stress and end-diastolic thickness since wall thickness is in the denominator in the equation used to calculate wall stress. Furthermore, increasing hypertrophy may cause mechanical interference and structural changes of the myocardium with adjacent myocardial fibers embedded in a fixed matrix of connective tissue,\textsuperscript{23} which may mutually impair their ability to increase systolic thickness. Changes in collagen architecture have been shown to be associated with depressed systolic function.\textsuperscript{24,25} Interestingly, these relations imply that in spite of reduced local systolic wall stress in the hypertrophied myocardium, as found in the current study, contractility is impaired. This observation is supported by two studies which demonstrated that whether or not hypertrophy is adequate or inadequate in terms of maintaining normal systolic wall stress, advanced myocardial hypertrophy leads to depression of contractility.\textsuperscript{26,27}

Limitations

In the present study a control group with normal wall thickness and stress was not included; however, we have previously shown that fractional thickening in non-hypertrophied regions of patients with LV hypertrophy was similar when compared to healthy controls and corrected for wall stress.\textsuperscript{7} Wall-thickness measurements were performed in 2D planes extracted from the 3D data set. This approach cannot trace the same material point of the myocardium during one heart cycle (translational and angulated motion of the vector of wall thickening), thus, myocardial thickness may have been measured at different sites during end-diastole and end-systole with some inaccuracy in the spatial distribution of wall-thickness measurements.

Conclusions

Our data suggest that women have less fractional thickening of the hypertrophied regions when these are compared with similarly hypertrophied myocardial regions in men. When both regional wall thickness and regional wall stress were matched, there were no gender differences in fractional thickening. Thus, the difference in systolic function is directly related to differences in wall stress. The similar stress-thickening relations in men and women further indicate that the two groups do not exhibit major differences in LV contractile function.

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