ASSOCIATION OF SYSTOLIC DYSFUNCTION WITH LEFT VENTRICULAR HYPERTROPHY AND DIASTOLIC DYSFUNCTION IN HYPERTENSIVE PATIENTS

ASOCIACIÓN DE DISFUNCIÓN SISTÓLICA CON HIPERTROFIA VENTRICULAR IZQUIERDA Y DISFUNCIÓN DIASTÓLICA EN PACIENTES HIPERTENSOS


Summary
Background: the presence of systolic dysfunction has not been well recognized in hypertensive patients (p). Objectives: The aim of this study is to demonstrate that hypertensive p with left ventricular hypertrophy (LVH) have systolic dysfunction, and that this functional alteration increases when it is associated to diastolic dysfunction (DD). Methods: descriptive cross-sectional study with prospectively-collected sample according to specified inclusion and exclusion criteria. Left ventricular function was evaluated with conventional echocardiography, mitral valvular orifice Doppler and tissue Doppler following international guidelines. The p were divided in four groups by the presence or absence of LVH and DD. Statistical analysis: students t tests and ANOVA test, statistical significance p<0,05. Results: 292 p were included, 130 p (51 %) LVH- DD-; 36 p (5,9 %) LVH- DD+; 87 p (37,6 %) LVH+ DD-; and 39 p (5,5 %) LVH+ DD+. Patients with diastolic dysfunction were older and more frequently of female sex, had greater systolic blood pressure and central aortic systolic blood pressure. The shortening rate of longitudinal myocardial fibers measured by tissue Doppler (s wave) were 6,3 +1,1 cm/sec in LVH+ DD+ p, 7,2+1,3 cm/sec in LVH+ DD- p, 6,8+1,2 cm/sec in LVH- DD+ p, and 7,8+0,6 cm/sec in LVH- DD- p (p<0,005). Conclusions: hypertensives p had systolic dysfunction when LVH is present and it is greater when it is associated to DD.

Key words: systolic dysfunction – left ventricular hypertrophy – diastolic dysfunction – tissue doppler

Resumen:
Introducción: La presencia de disfunción sistólica no ha sido reconocida en pacientes (p) hipertensos. Objetivos: El objetivo del presente estudio es demostrar que los p hipertensos con hipertrofia ventricular izquierda (HVI) presentan disfunción sistólica, y que ella se incrementa cuando se asocia a disfunción diastólica (DD). Material y métodos: estudio observacional de corte transversal con la muestra recolectada en forma prospectiva de acuerdo a criterios de inclusión y exclusión preestablecidos. La función ventricular izquierda fue evaluada por ecocardiografía convencional, Doppler del orificio valvular mitral y Doppler tisular siguiendo las normativas internacionales. Los p fueron divididos en cuatro grupos de acuerdo a la presencia o ausencia de HVI y DD. Análisis estadístico: test t de students y test de ANOVA, significación estadística p<0,05. Resultados: se incluyeron 292 p, 130 p (51 %) HVI- DD-; 36 p (5,9 %) HVI- DD+; 87 p (37,6 %) HVI+ DD-; y 39 p (5,5 %) HVI+ DD+. Los p con DD fueron de mayor edad, más frecuentemente mujeres, y su PA sistólica y presión aórtica central estaban más elevados. La velocidad de acortamiento longitudinal de las fibras miocárdicas, medida como onda s con Doppler tisular fue 6,3 +1,1 cm/sec en p HVI+ DD+, 7,2+1,3 cm/sec en p HVI+ DD-, y 7,8+0,6 cm/sec en p HVI- DD+ (p<0,005). Conclusiones: los p hipertensos presentan disfunción sistólica cuando la HVI está presente y es mayor cuando se asocia a DD.

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Introduction

Adult cardiac tissues contain relatively more alpha myosin heavy chains (MyHC-alpha) than beta myosin heavy chains (MyHC-beta), and pathological hypertrophy is characterized by changes in gene expression with reduced MyHC-alpha and increased MyHC-beta, a molecular phenomenon also called fetal reprogramming. At the same time, a decrease of SERCA (sarco-endoplasmic reticulum Ca2 ATPase) can be observed, this ATPase has ability to recapture calcium in the lumen of the sarcoplasmic reticulum of myocytes, and the release and reuptake of calcium in the sarcoplasmic reticulum regulates the frequency of contraction and relaxation of the myocardial fibers. For these reasons, different stimuli acting on myocytes could generate a left ventricular hypertrophy response, with phenotypic changes in sarcomere proteins expression with a pattern similar to the fetal cells. The MyHC-alpha is characterized by a fast shrinkage while MyHC-beta, by contrast, has a slow contraction. That is why, when an isolated hypertrophic myocytes is compared with a normal one, time to peak systolic contraction and time to peak diastolic relaxation are higher in the former than in the later, and this type of evidence shows that in the isolated hypertrophic myocytes inotropic and diastolic relaxation properties are altered. Furthermore, apoptosis is abnormally stimulated in the myocardium of patients with essential hypertension, and increased apoptosis has been observed in human left ventricular hypertrophy. At the same time, coronary flow reserve is reduced in hypertensive patients, both in the absence but particularly in the presence of left ventricular hypertrophy. This is due both to an increased vascular resistance due to the high left ventricular intracavitary pressure and perivascular compression of resistance vessels, as well as a marked reduction in the density of capillaries and arterioles by the increase in wall mass and decreased vascular area section, as well as the expansion of the perivascular extracellular matrix. At the same time, an overproduction of free radicals of oxygen develope, with destruction of nitric oxide and increased oxidative stress, so that the vascular endothelium-dependent relaxation is altered. This endothelial dysfunction is associated with hypertrophy, and the larger the left ventricular mass index the lower is the vasodilator response to acetylcholine. Consequently, the development of systolic dysfunction in hypertensive patients with left ventricular hypertrophy could be possible. However, studies like HyperGEN, in which only 14 % of hypertensive patients had moderate or severe systolic dysfunction, are contrasted with these pathophysiological speculations. In the same way, a study in which 38 healthy controls were compared to 38 hypertensive patients, although standard 2D echo Doppler and real time 3D echocardiography assessment showed that the left ventricular mass index was greater and the diastolic function was worst in the last group, the ejection fraction and the stroke volume were not significantly different between both groups. With this background, we hypothesized that hypertensive patients with left ventricular hypertrophy, both in the absence and presence of diastolic dysfunction, but even in this case, have a systolic dysfunction that the newly emerging imaging technologies could unmask.

The aim of this study is to demonstrate that hypertensive patients with left ventricular hypertrophy have systolic dysfunction, and that this functional alteration increases when it is associated to diastolic dysfunction.

Methods

This is a descriptive cross-sectional study, with a prospectively collected sample conducted at the Cardiology Institute of the Sanatorio Británico SA in Rosario, Argentina. The study has been carried out in accordance with the Code of Ethics of the World Medical Association for experiments involving humans. Inclusion criteria were:

1) essential arterial hypertensive patient over 18 years of age, both sexes at their first consultation,
2) 2D and M Mode echocardiography, mitral Doppler and tissue Doppler of sufficient quality to perform the calculation of the LV mass and evaluate LV diastolic and systolic function.

Exclusion criteria were:

1) clinical cardiovascular disease that could impact the development of left ventricular hypertrophy or ventricular dysfunction, such as aortic or mitral valve disease, congenital heart disease, renal insufficiency, morbid obesity or thyroid disease
2) prior clinical diagnosis of heart failure syndrome
3) medical history of ischemic heart disease or prior diagnosis of coronary artery disease,
4) treatmen twith drugs that affect heart rate and rest,
5) rhythm disturbances like right or left bundle branch block, atrio-ventricular block, pre-excitation syndrome, or supraventricular arrhythmias.

For the diagnosis of hypertension the 2013 European Society of Hypertension/European Socie-
ty of Cardiology Guidelines for the Management of Arterial Hypertension criteria was applied (12). Clinical arterial blood pressure was measured with a digital sphygmomanometer (OMRON model HEM-705CPINT), and the average of three consecutive measurements 1 minute apart after 5 minutes in the sitting position is reported. The central aortic systolic blood pressure was measured non invasively with an internationally validated radial pulse tonometer that by a mathematical transferfunction automatically calculates the value. The tonometer was placed over the radial artery in the dominant arm, which was the one where the higher systolic blood pressure was obtained, and was calibrated according to the average of three over five brachial blood pressure measurements with a difference between them less than 10mmHg for systolic pressure and 5mmHg for diastolic pressure. Three readings of 10 seconds duration each were performed, and the average value of them was the central aortic systolic pressure reported. The ultrasound studies were performed with a General Electric System Five ultrasound scanner provided by harmonic capability with a 2.5 MHz phase array multifrequency transducer with standardized protocol and conducting a tissue Doppler study by DP. The intraobserver variability was previously tested, and the concordance was acceptable (13). The left ventricular mass was assessed by the method of Devereux and indexed by body surface, and left ventricular hypertrophy was considered when its value was greater than 95 g/m2 in women and 115 g/m2 in men (14-15). Diastolic function was assessed by conventional Doppler of the mitral valve orifice corrected by age and tissue Doppler of the interventricular septum and lateral wall at the mitral annulus level in the apical 4 chamber conventional view, and diastolic dysfunction was diagnosed with a relationship between transmitral diastolic peak early flow velocity to the average of the peak early diastolic relaxation velocity at the septal and lateral mitral annulus E/e’ > 13. Systolic function was assessed by the rate of systolic excursion (s wave) of the interventricular septum at the mitral annulus level in cm/sec with tissue Doppler. End diastolic volume (EDV), end systolic volume (ESV), ejection fraction (EF) and stroke volume (SV) were assessed by the modified Simpson biplane method and measured in ml and cardiac work (CW) was measured in gers/min; and all were corrected by body surface area (16-17). Patients were divided into four groups according to the presence or absence of left ventricular hypertrophy and diastolic dysfunction: 1) left ventricular hypertrophy and diastolic dysfunction present (LVH+ DD+), 2) left ventricular hypertrophy absent and diastolic dysfunction present (LVH-DD+), 3) left ventricular hypertrophy absent and diastolic dysfunction present (LVH- DD+), and 4) left ventricular hypertrophy and diastolic dysfunction absent (LVH- DD-).

Statistical analysis: Continuous variables are reported as means with their standard deviations, and discrete variables as absolute values and percentages. Student test for differences in means and proportions and ANOVA test were applied, considering statistical significance a value of p<0.05.

**Results**

The study included 292 consecutive patients between February 21, 2011 and February 28, 2013, of which 142 patients (48.6%) were male, the mean age of the sample was 60.1±12.7 years. Of all patients, 75 (25.7%) had diastolic dysfunction according to the applied criteria and 126 (43.2%) had left ventricular hypertrophy. Figure 1 shows the patients belonging to the four predetermined groups.

![Diagram](image-url)

Patients with diastolic dysfunction were older and more frequently of female sex, had greater systolic blood pressure and central aortic systolic blood pressure (Table 1).

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>LVH+ DD+</th>
<th>LVH- DD+</th>
<th>LVH+ DD-</th>
<th>LVH- DD-</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEAN AGE</td>
<td>69.4 ± 9</td>
<td>64.3 ± 9</td>
<td>60.6 ± 13</td>
<td>56.0 ± 13</td>
</tr>
<tr>
<td>MALES n - %</td>
<td>10 - 25.6</td>
<td>10 - 27.8</td>
<td>55 - 63.2</td>
<td>67 - 51.5</td>
</tr>
<tr>
<td>BMI kg/m2</td>
<td>27.8 ± 7.4</td>
<td>27 ± 3.7</td>
<td>30.9 ± 6.6</td>
<td>27.1 ± 4.3</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>147 ± 24</td>
<td>139 ± 17</td>
<td>139 ± 16</td>
<td>136 ± 16</td>
</tr>
<tr>
<td>DBP mm Hg</td>
<td>75 ± 13</td>
<td>73 ± 11</td>
<td>78 ± 12</td>
<td>79 ± 9</td>
</tr>
<tr>
<td>CaoP mm Hg</td>
<td>131 ± 17**</td>
<td>119 ± 13</td>
<td>121 ± 14</td>
<td>119 ± 13</td>
</tr>
</tbody>
</table>

*p<0.0025 vs LVH+ DD+; **p<0.025 vs LVH+ DD+; +p<0.05 vs other three groups; *p<0.0005 vs LVH+ DD+ and LVH- DD+.
End diastolic volume, stroke volume and cardiac work index were significantly higher in both groups with left ventricular hypertrophy compared to both groups without target organ damage (p<0.005), while patients with left ventricular hypertrophy and without diastolic dysfunction had significantly higher end systolic volume (p<0.05). Left ventricular ejection fraction was not significantly different between the four groups (Table 2).

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>LVH+ DD+</th>
<th>LVH- DD+</th>
<th>LVH+ DD-</th>
<th>LVH- DD-</th>
</tr>
</thead>
<tbody>
<tr>
<td>EjF %</td>
<td>68.2 ± 8.5</td>
<td>65.6 ± 8.5</td>
<td>66.2 ± 8.5</td>
<td>65.3 ± 9.8</td>
</tr>
<tr>
<td>EDV ml/2</td>
<td>67.4 ± 13.9*</td>
<td>57.5 ± 10.4</td>
<td>68.9 ± 13.6*</td>
<td>56.9 ± 10.9</td>
</tr>
<tr>
<td>ESV ml/2</td>
<td>21.4 ± 18.6 ± 16.6 ± 8.2*</td>
<td>18.6 ± 5.8</td>
<td>23.5 ± 20 ± 7.3</td>
<td></td>
</tr>
<tr>
<td>SV ml/2M</td>
<td>46 ± 45.4 ± 9.8*</td>
<td>36.9 ± 37 ± 7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CWP g/s/M</td>
<td>27.7 ± 24.1</td>
<td>21.8*</td>
<td>19.2</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.005 LVH vs no LVH; +p<0.05 LVH+ DD+ vs LVH- DD-

The average rate of systolic excursion(s-wave) of the interventricular septum and lateral wall with tissue Doppler at the mitral annulus level was 7.5±5.2 cm/s in patients without left ventricular hypertrophy, and 6.9±1.3 cm/s in patients with left ventricular hypertrophy (p <0.05), while it was 7.2±1.5 cm/s in patients with diastolic dysfunction and 6.4±1.3 cm/s in patients with diastolic dysfunction (p<0.05). Figure 2 shows the average rate of systolic excursion of the interventricular septum and lateral wall at the mitral annulus level with tissue Doppler in the four groups.

**Discussion**

This study confirms the hypothesis that in hypertensive patients the presence of left ventricular hypertrophy, associated or not to diastolic dysfunction, as well as the detection of diastolic dysfunction in the presence or absence of left ventricular hypertrophy, are associated to a reduced rate of shortening of the longitudinal left ventricular myocardial fibers significantly, and therefore, these patients could have reduced systolic function of the left ventricle. Although left ventricular hypertrophy and diastolic dysfunction affect different parameters of left ventricular systolic function, the combination of both phenomena is the scenario with further deterioration of left ventricular inotropic properties.

The left ventricle has longitudinal, circumferential and radial muscle fibers. During the cardiac cycle a systolic shortening of the longitudinal fibers, and an early systolic torsion of the left ventricle, followed by an early diastolic movement in opposite directions about the long axis of the heart, due to rotation directed in opposite directions from the apical and basal segments could be detected. The characteristics of this torsion have been described in different clinical studies, and it is well established that these shortening movements and left ventricular rotation are sensitive to changes in both segmental and global function. LVH adversely affects the shortening of the fibers along the longitudinal and torsional movement, and these abnormalities may be a new marker for evaluating pathological alterations of left ventricular function (18-19).

Recently, the E/e´ ratio, the parameter used in this study for the diagnosis of diastolic dysfunction, was shown to be more correlated than mitral E/A ratio to 3DE left ventricular speckle tracking and the left ventricular untwisting rate. The E/e´ ratio was an independent predictor of global area strain, global circumferential strain, global radial strain, global longitudinal strain, and left ventricular untwisting in 147 newly diagnosed untreated hypertensive patients (20). So the study by Tadic et al demonstrated a sharp association between the E/e´ ratio, a parameter with good evidence as a marker of an elevation of left ventricular end diastolic pressure and diastolic dysfunction and a reduced rate of shortening of the left ventricular longitudinal myocardial fibers, although they failed to show this data by pulse and tissue Doppler imaging as in the present study. However, in another study in which 18 young newly diagnosed and never treated hypertensive patients underwent pulse tissue Doppler of the mitral annulus and speckle tracking echocardiography, and even without differences in left ventricular ejection fraction with regard to the controls, the annular systolic velocity (s wave), the early diastolic velocity (e´), and the global longitudinal strain were lower as well as the E/e´ ratio was higher in patients.
with hypertension. The results of this study are in the same direction of the data obtained by our group, confirming the early compromise of both systolic and diastolic function in hypertensive patients, mostly of the longitudinal left ventricular fibers, and the authors concluded that a highly significant association between left ventricular diastolic function and global longitudinal strain independently of afterload and the degree of left ventricular hypertrophy is evident since the very beginning of hypertension (21).

The presence of the clinical syndrome of heart failure beyond that systolic function is preserved or not, seems to be the most relevant information about the prognosis of patients with this condition, and several epidemiological studies have failed to confirm that the depressed ejection fraction indicate an increased cardiovascular risk in patients in this clinical setting (22-23). Moreover, the diagnosis of diastolic dysfunction is an imaging characterization, whose clinical relevance is significative because as the Olmsted County Heart Function Study showed, in which during 4 years of follow two ultrasonography studies were performed to the patients who were divided into three groups: those whose diastolic function normalized or remained normal, those who progressed to mild diastolic dysfunction or remained with mild diastolic dysfunction, and those whose diastolic function remained or progressed to moderate to severe dysfunction, it is associated with the incidence of heart failure during a follow-up of 6 years after adjustment for age, hypertension, diabetes or coronary artery disease (24).

In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) almost 10% of the sample was enrolled in an echocardiography sub study, in which the patients were classified according to the presence of left ventricular hypertrophy and a concentricity index in four groups: dilated and nondilated eccentric hypertrophy and dilated and nondilated concentric hypertrophy. Patients with concentric dilated left ventricular hypertrophy had lower ejection fraction and higher left ventricular mass index, stroke volume, left ventricular midwall shortening, left atrial volume, and isovolumic relaxation time compared to patients with concentric nondilated LVH, as well as the data obtained in patients with eccentric dilated LVH compared to patients with eccentric non dilated LVH were in the same direction. This trial reflects that specific types of left ventricular remodeling in response to hypertension had reduced systolic function, supporting the results of our group study in which patients with LVH and/or diastolic dysfunction had tissue Doppler evidence of systolic dysfunction (25-26).

In another study, LV dyssynchrony was assessed with 2-D and Doppler echocardiography and pulse tissue Doppler imaging in hypertensive patients with normal systolic function (ejection fraction > 50%), without the clinical syndrome of congestive heart failure and QRS duration <120 msec. A maximal difference of 50 msec in the time intervals from onset of the QRS complex to the peak systolic velocity on the pulsed tissue Doppler waveform between any 2 opposing LV walls, which exceeded 2 standard deviations of the mean value in a control group was considered for defining dyssynchrony. Left ventricular dyssynchrony was detected in 47,6% of the patients and a septal to lateral delay was identified in 57,1% of the cases, and both were associated with left ventricular mass index, left atrial volume index and left ventricular sphericity. This study provides further insight into the effects of hypertension on LV function and the potential mechanism to explain the reduced systolic function in LV hypertrophy or diastolic dysfunction in hypertensive patients (27). In a similar scenario, a group of 41 normotensive controls was compared with a group of 84 hypertensive patients, and the frequency of dyssynchrony was 40,5% in the last and 19,5% in the controls considering at least one of the following echocardiography cutoff criteria: delay greater than 78 milliseconds between the shortest and longest time to peak systolic velocity in the six basal segment, standard deviation greater than 34,5 milliseconds in the time to the peak systolic velocity in the 6 basal segments, or a maximum delay of 60 milliseconds between the time to peak systolic velocity in the ventricular septum to the lateral wall at the basal level, moreover, LV dyssynchrony was found in 20% of no hypertrophy hypertensive patients, in 42% of mild hypertrophy hypertensive patients and in 75% of hypertensive patients with moderate hypertrophy, so that the frequency of dyssynchrony increased as the severity of the LV hypertrophy was greater (28).

The effect of blood pressure variability on left ventricular systolic function was evaluated in 309 consecutive non treated outpatients of less than 6 months primary hypertension diagnosis with an ejection fraction > 55%. Blood pressure variability was assessed as the standard deviation of awake systolic blood pressure and as weighted standard deviation of 24 hours systolic blood pressure,
while systolic LV function was evaluated by echocardiography measuring midwall fractional shortening, circumferential end systolic stress, peak systolic wall stress, and left ventricular fractional shortening. The patients with high blood pressure variability (values over the mean of the sample) had significantly higher left ventricular mass index, circumferential end systolic wall stress and peak systolic wall stress and significantly less midwall fractional shortening – circumferential end systolic wall stress ratio. This study shows the early involvement of left ventricle as target organ damage in hypertension and the development of left ventricular systolic dysfunction since the very beginning of the disease, even when left ventricular hypertrophy is not present (29). The myocardial collagen turnover could be one of the explanations of these early alterations of the left ventricular systolic function. In a group of untreated hypertensive patients with an ejection fraction greater than 55 % the serum levels of the aminoterminal propeptide of procollagen I/III and tissue inhibitor of matrix metalloproteinase (TIMP-1) correlated to the longitudinal and basal to apical torsion measured by speckle tracking method. This study showed that the myocardial fibrotic process affects very early in the evolution of hypertension the contractile function of the left ventricle, highlighting that the functional alterations have a structural substrate (30).

Conclusions
This study establishes that in hypertensive patients with left ventricular hypertrophy, regardless of whether it is associated with diastolic dysfunction, systolic function is depressed, and on the other hand, hypertensive patients without left ventricular hypertrophy but with diastolic dysfunction also have impaired contractile function. These findings require us to rethink concepts deeply rooted, since in reality, the clinical syndrome of heart failure in subjects with a substrate of diastolic dysfunction could be a subclinical condition of systolic dysfunction, undiagnosed by conventional algorithms, and on the other hand, in individuals with clinical syndrome of heart failure with preserved ejection fraction should be considered that the left myocardial-inotropic properties are altered, and this could be the true background of the pathogenesis.

References
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