Ventricular-Arterial Coupling in Severe Aortic Stenosis: Relationship with Symptoms and Heart Failure

Cupla ventrí culo-arterial en la estenosis aórtica grave: relación con los síntomas y con insuficiencia cardíaca

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ABSTRACT

Background: Left ventricular function is determined by ventricular-arterial coupling via effective arterial elastance (Ea) and left ventricular end-systolic elastance (Ees). In aortic stenosis, the characteristics of the vascular system may influence left ventricular function, particularly in patients with symptoms or heart failure.

Objective: The aim of the present study was to evaluate ventricular-arterial coupling using the Ea/Ees ratio in patients with severe aortic stenosis and its relationship with symptoms and heart failure.

Methods: The cohort consisted of 136 patients aged 69±11 years, with severe aortic stenosis (aortic valve area <1 cm²). Ea and Ees were estimated noninvasively. Patients were divided into three groups: heart failure (n=48), symptomatic (n=45) and asymptomatic (n=43).

Results: Ea was increased in patients with heart failure while Ees was significantly reduced in patients with symptoms and with heart failure compared with asymptomatic ones. The Ea/Ees ratio was significantly higher in symptomatic and heart failure patients compared with asymptomatic patients (1.5±1.3 and 0.81±0.49 vs. 0.61±0.37; p<0.01). There were no significant differences in aortic valve area among groups.

Conclusions: The Ea/Ees ratio was increased in patients with symptoms or heart failure due to increased Ea and reduced Ees. The development of symptoms or heart failure in severe aortic stenosis seems to be related with the characteristics of the vascular system, irrespectively of aortic stenosis severity.

Key words: Aortic Stenosis - Echocardiography - Ventricular-arterial Coupling

RESUMEN

Introducción: La función del ventrículo izquierdo está determinada por el acoplamiento entre la elastancia arterial efectiva (Ea) y la elastancia de fin de sistole del ventrículo izquierdo (Efs). En la estenosis aórtica, las características de la vasculatura pueden influir sobre la función del ventrículo izquierdo, especialmente en pacientes con síntomas o insuficiencia cardíaca.

Objetivo: Evaluar la cupla ventriculoarterial mediante la relación Ea/Efs en pacientes con estenosis aórtica grave y su relación con los síntomas y con insuficiencia cardíaca.

Material y métodos: Se incluyeron 136 pacientes, con edad promedio de 69 ± 11 años, portadores de estenosis aórtica grave (área valvular aórtica < 1 cm²). La Ea y la Efs se estimaron en forma no invasiva. Los pacientes se dividieron en tres grupos: insuficiencia cardíaca (n = 48), sintomáticos (n = 45) y asintomáticos (n = 43).

Resultados: La Ea se observó incrementada en los pacientes con insuficiencia cardíaca, mientras que la Efs estuvo significativamente disminuida en los pacientes sintomáticos y con insuficiencia cardíaca respecto de los asintomáticos. La relación Ea/Efs fue significativamente mayor en los pacientes sintomáticos y con insuficiencia cardíaca en comparación con los pacientes asintomáticos (1,5 ± 1,3 y 0,81 ± 0,49 vs. 0,61 ± 0,37; < 0,01). No hubo diferencias en el área valvular aórtica entre los grupos.

Conclusiones: La relación Ea/Efs estuvo incrementada en pacientes con síntomas o insuficiencia cardíaca debido al incremento de la Ea y la disminución de la Efs. La aparición de síntomas o de insuficiencia cardíaca en la estenosis aórtica grave parece estar relacionada con las características de la vasculatura, independientemente de la gravedad de la estenosis valvular.

Palabras clave: Estenosis aórtica - Ecocardiografía - Cupla ventriculoarterial

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† To apply as Full Member of the Argentine Society of Cardiology
INTRODUCTION

Aortic stenosis (AS) is one of the most common valvular heart diseases and its incidence is continuously increasing in the adult population. (1) The development of symptoms in severe AS (angina, dyspnea and syncope) is associated with higher mortality (75%) at 5 years. (2) The progression of class I-II dyspnea to class III–IV associated with signs of congestive heart failure (HF) indicates worse outcome. (3) The presence of HF in AS is more frequently associated with decreased left ventricular (LV) ejection fraction (EF) due to impaired contractile function or excessive afterload (mismatch) with or without significant coronary artery disease. (4) However, chronic LV pressure overload may lead to HF in patients with preserved EF despite having similar geometry and indexes of systolic function to those of patients without clinical HF. (5) In different studies, the presence of symptoms or HF could not be correlated with aortic valve area (AVA) or with parameters of LV function. (6, 7) This could be explained considering that LV overload is not only represented by valvular stenosis but also by an increased arterial load in patients with predominantly degenerative AS, and by the high prevalence of hypertension (60–75%) and other cardiovascular risk factors, as diabetes, dyslipidemia and smoking habits. (8) Left ventricular function does not only depend on the intrinsic properties of the LV (contractility, geometry and preload) but also on the characteristics of the vascular system receiving the stroke volume (SV) ejected, which can be evaluated through ventricular-arterial coupling (VAC), the ratio between effective arterial elastance (Ea) and left ventricular end-systolic elastance (Ees) (Ea/Ees ratio). (9) Ees is a parameter that estimates the performance of left ventricular contractility and is relatively independent of loading conditions. (10) Ea evaluates the characteristics of the arterial system and is influenced by aortic impedance, peripheral resistance and pulsatile flow. (11) Although VAC has been evaluated with mathematical and experimental models, (12, 13) its correlation with the presence of symptoms of HF in AS has not been established. The aim of the present study was to evaluate VAC in patients with severe AS and its relationship with symptoms or development of HF.

METHODS

The cohort consisted of 136 patients (82 men and 54 women, mean age 69±11 years), with severe aortic stenosis, defined as aortic valve area (AVA) <1 cm², undergoing Doppler-echocardiography. Patients with moderate to severe aortic or mitral regurgitation were excluded. History of ischemic heart disease was based on the presence of at least one of the following criteria: 1) history of myocardial infarction, percutaneous coronary intervention or myocardial revascularization surgery, 2) coronary artery stenosis >50% documented by angiography, and 3) akinetic segments documented by echocardiography. Data from coronary angiography in 54 patients showed that 24 patients had coronary artery disease. All patients underwent complete anamnesis to detect the presence of coronary risk factors and symptoms, cardiovascular physical examination, blood pressure measurement, recording of carotid artery pulse waveform and complete Doppler echocardiography.

Echocardiogram and Doppler echocardiography

The study was performed with a TOSHIBA SSH140A ultrasound machine using 2.5 MHz transducer and an ESAOTE Mylab 50 ultrasound machine with 2.5 to 3 MHz transducer, with the patient in left lateral decubitus position and simultaneous recording of lead II electrocardiogram as reference. M mode two-dimensional echocardiography was used to calculate LV endocardial fractional shortening (eFS), relative wall thickness (RWT), end-diastolic volume (EDV) using the area-length method, end-systolic volume (ESV), ejection fraction (EF), stroke volume index (SVI) and left atrial volume index (LAVI) according to the American Society of Echocardiography (ASE) criteria. (14) Midwall fractional shortening (mFS) was estimated using the Kioide formula. (15, 16) Left ventricular mass was calculated using the Devereux formula (17) and mass index as mass indexed for body surface area (LVMI). Peak gradient (PG) and mean gradient (MG) across the aortic valve and the aortic velocity-time integral (TVI) were recorded with continuous Doppler echocardiography from the apical, right parasternal, subcostal and suprasternal views. The average of three consecutive measurements was considered for each parameter.

Calibrated carotid pulse tracing

After echocardiography, the carotid pulse tracing was recorded with a TPW-01 A pulse transducer and blood pressure was measured in the right arm with the use of an arm-cuff sphygmomanometer, with the patient in left lateral decubitus position. Calibration of the carotid pulse tracing was carried out according to the method used in our laboratory (18) to obtain end-systolic pressure (ESP).
by sphygmomanometry.

The estimation of V0 is more accurate using the data obtained near the onset of the ejective period. Thus, tn was determined by the ratio between the pre-ejective period (peak of the R wave at the onset of ejection) and the total systolic period (peak of the R wave at end-systole) with end-systole defined by the velocity-time integral in the LV outflow tract obtained by pulsed Doppler echocardiography. Its value ranges between 0.25 and 0.35, and En was obtained from the average values of Sanzaki et al. Ea was calculated as the

### Table 1. Baseline patient characteristics and echocardiographic results

<table>
<thead>
<tr>
<th></th>
<th>AS with HF (n=48)</th>
<th>Symptomatic AS (n=45)</th>
<th>Asymptomatic AS (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>71±11</td>
<td>67±11</td>
<td>67±12</td>
</tr>
<tr>
<td>Men/women</td>
<td>31/17</td>
<td>27/18</td>
<td>21/22</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.82±0.2</td>
<td>1.85±0.2</td>
<td>1.83±0.23</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>18 (37)*</td>
<td>12 (27) **</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>32 (67)*</td>
<td>39 (87)**</td>
<td>12 (28)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (21)*</td>
<td>10 (22)**</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12 (25)</td>
<td>17 (38)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Smoking</td>
<td>11 (23)#</td>
<td>20 (44)**</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>48 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I-II dyspnea</td>
<td>21 (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III-IV dyspnea</td>
<td>8 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>123±22</td>
<td>131±24</td>
<td>131±21</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73±14</td>
<td>75±11</td>
<td>78±13</td>
</tr>
<tr>
<td>End-systolic pressure, mm Hg</td>
<td>91±16</td>
<td>92±15</td>
<td>94±12</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>37±16**</td>
<td>51±17†</td>
<td>62±13</td>
</tr>
<tr>
<td>Ejection fraction ≥50 %, n, (%)</td>
<td>9 (19)</td>
<td>20 (44)</td>
<td>30 (70%)</td>
</tr>
<tr>
<td>End-diastolic volume, ml</td>
<td>158±62†</td>
<td>116±57</td>
<td>100±45</td>
</tr>
<tr>
<td>End-systolic volume, ml</td>
<td>106±58**</td>
<td>58±47†</td>
<td>41±32</td>
</tr>
<tr>
<td>Endocardial fractional shortening, %</td>
<td>25±10†</td>
<td>32±10†</td>
<td>37±9</td>
</tr>
<tr>
<td>Midwall fractional shortening, %</td>
<td>14±6†</td>
<td>16±6§</td>
<td>19±6</td>
</tr>
<tr>
<td>LV diastolic dimension, cm</td>
<td>5.5±0.9†</td>
<td>5.3±0.9</td>
<td>5.1±0.7</td>
</tr>
<tr>
<td>LV systolic dimension, cm</td>
<td>4±1†</td>
<td>3.6±1§</td>
<td>3.2±0.8</td>
</tr>
<tr>
<td>Body mass index, g/m²</td>
<td>174±50†</td>
<td>164±46</td>
<td>150±43</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.44±0.12‡</td>
<td>0.50±0.11</td>
<td>0.49±0.11</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.63±0.21</td>
<td>0.65±0.22</td>
<td>0.70±0.19</td>
</tr>
<tr>
<td>Peak gradient, mm Hg</td>
<td>62±31#</td>
<td>76±30</td>
<td>70±27</td>
</tr>
<tr>
<td>Mean gradient, mm Hg</td>
<td>36±19#</td>
<td>44±18</td>
<td>41±17</td>
</tr>
<tr>
<td>Stroke volume index, ml/m²</td>
<td>27±9‡</td>
<td>34±12</td>
<td>38±10</td>
</tr>
<tr>
<td>LA volume index, ml/m²</td>
<td>60±16‡</td>
<td>48±11</td>
<td>49±15</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>23±13‡</td>
<td>16±6</td>
<td>14±5</td>
</tr>
<tr>
<td>Volume axis intercept at zero pressure, ml</td>
<td>47±91‡</td>
<td>13±42§</td>
<td>-0.75±31</td>
</tr>
<tr>
<td>Ea, mm Hg/ml</td>
<td>3.8±1.6‡</td>
<td>3±1</td>
<td>2.8±1</td>
</tr>
<tr>
<td>Ees, mm Hg/ml</td>
<td>2.1±1.2†</td>
<td>2.1±1§</td>
<td>3.2±1</td>
</tr>
<tr>
<td>Ventricular-arterial coupling (Ea/ Ees)</td>
<td>1.5±1.3#</td>
<td>0.81±0.49§</td>
<td>0.61±0.37</td>
</tr>
</tbody>
</table>

HF vs. asymptomatic: * <0.05; † <0.01; † < 0.0001
HF vs. symptomatic: # < 0.01; §§ <0.0001
Symptomatic vs. asymptomatic: ** <0.05; ¶ < 0.02; § <0.001


### Assessment of end-systolic elastance, effective arterial elastance and ventricular-arterial coupling

End-systolic elastance was estimated by the method by Sanzaki et al. [19]

Considering that:

\[
Ees = \frac{ESP}{(ESV - V0)}
\]

and

\[
V0 = \left[\frac{(ESV \times ESP) - (EDV \times n(tn))}{(dP/ESP) - (En (tn))}\right]
\]

where dP corresponds to the diastolic pressure obtained by sphygmomanometry.

The estimation of V0 is more accurate using the data obtained near the onset of the ejective period. Thus, tn was determined by the ratio between the pre-ejective period (peak of the R wave at the onset of ejection) and the total systolic period (peak of the R wave at end-systole) with end-systole defined by the velocity-time integral in the LV outflow tract obtained by pulsed Doppler echocardiography. Its value ranges between 0.25 and 0.35, and En was obtained from the average values of Sanzaki et al. Ea was calculated as the
VENTRICULAR-ARTERIAL COUPLING IN SEVERE AORTIC STENOSIS / Ricardo A. Migliore et al.

The main finding of this study is that VAC was impaired not only in patients with AS HF but also in those with S AS, with a significant difference compared with patients with A AS, implicating a progressive decrease from the asymptomatic stage of the disease to the decompensated stage with HF. Ventricular-arterial coupling evaluates the efficiency of LV systolic function in relation with the characteristics of the vascular system into which the SV is ejected, expressed by the Ea/Ees ratio. Ees, initially described by Suga and Sagawa, (22) estimates the LV chamber contractile state through the slope of the end-systolic linear relationship, obtained using a conductance catheter invasively placed in the LV for simultaneous recording of ventricular pressure and volume during the diastolic filling period. Ea divided by Ees.

Assessment of aortic stenosis
The effective AVA was calculated using the continuity equation. (20)

Assessment of left ventricular diastolic function
Mean LA pressure was estimated as the relationship between peak velocity of the E mitral wave and peak velocity of the average E′ wave measured at the lateral and septal mitral annulus using tissue Doppler imaging (E/E′ ratio). (21)

The patients were divided into three groups: AS with HF (AS HF; n=48) (NYHA class III-IV dyspnea), symptomatic AS (S AS; n=45) (class I-II dyspnea, angina or syncope), and asymptomatic AS (A AS) (n=43).

Statistical analysis
Continuous variables were expressed as mean ± standard deviation, and groups were compared with one-way analysis of variance using Snedecor’s F distribution, followed by the Bonferroni test. All the calculations were performed using Statistix 7.0 software package. A p value <0.05 was considered statistically significant.

Ethical considerations
The protocol was approved by the Research Committee of the Hospital Eva Perón.

RESULTS
The distribution of age, sex, body surface area, systolic blood pressure, diastolic blood pressure and end-systolic pressure was similar among groups (Table 1). Coronary artery disease, hypertension and diabetes were more frequent in the AS HF and S AS groups. Tobacco use was more prevalent in the S AS group. The prevalence of angina, dyspnea and syncope in the S AS group was in accordance with previous reports. A significant reduction was observed in EF, eFS and mFS in the AS HF group and S AS group compared with the A AS group, and the differences between the two former groups were also significant. End-systolic volume and LV systolic dimension also presented significant differences in the three groups, but EDV, LV diastolic dimension, LVMi and RWT were only abnormal in patients with AS HF. The AVA was similar in the three groups, but PG, MG and SVI were reduced in patients with AS HF. In the assessment of diastolic function, LA volume index and E/E′ ratio were higher in patients with AS HF, but there were no significant differences in patients with or without symptoms.

Ventricular-arterial coupling
Ea was significantly higher only in patients with AS HF. Ees was significantly reduced in patients with S AS and AS HF. V0 was greater in patients with AS HF, although patients with S AS also presented higher V0 compared with those with A AS. Ventricular-arterial coupling, measured as the Ea/Ees ratio, was increased in patients with AS HF and S AS, with significant differences between both groups (Figure 1).

DISCUSSION
The main finding of this study is that VAC was impaired not only in patients with AS HF but also in those with S AS, with a significant difference compared with patients with A AS, implicating a progressive decrease from the asymptomatic stage of the disease to the decompensated stage with HF. Ventricular-arterial coupling evaluates the efficiency of LV systolic function in relation with the characteristics of the vascular system into which the SV is ejected, expressed by the Ea/Ees ratio. Ees, initially described by Suga and Sagawa, (22) estimates the LV chamber contractile state through the slope of the end-systolic linear relationship, obtained using a conductance catheter invasively placed in the LV for simultaneous recording of ventricular pressure and volume during

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>NYHA Class</th>
<th>E/E' Ratio</th>
<th>End-Systolic Pressure (ESP)</th>
<th>End-Systolic Volume (ESV)</th>
<th>LV Mass Index (LVMi)</th>
<th>Right Ventricular Wall Thickness (RWT)</th>
<th>EF (%)</th>
<th>eFS (%)</th>
<th>mFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS HF</td>
<td>III-IV</td>
<td>2.5 ± 0.7</td>
<td>70 ± 15</td>
<td>130 ± 30</td>
<td>100 ± 5</td>
<td>0.45 ± 0.1</td>
<td>50</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>A AS</td>
<td>I-II</td>
<td>1.5 ± 0.3</td>
<td>50 ± 10</td>
<td>80 ± 20</td>
<td>70 ± 3</td>
<td>0.35 ± 0.1</td>
<td>60</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>S AS</td>
<td>I-II</td>
<td>0.8 ± 0.4</td>
<td>30 ± 5</td>
<td>60 ± 15</td>
<td>60 ± 2</td>
<td>0.25 ± 0.1</td>
<td>70</td>
<td>40</td>
<td>35</td>
</tr>
</tbody>
</table>

#### Statistical Analysis
Continuous variables were expressed as mean ± standard deviation, and groups were compared with one-way analysis of variance using Snedecor’s F distribution, followed by the Bonferroni test. All the calculations were performed using Statistix 7.0 software package. A p value <0.05 was considered statistically significant.

#### Ethical Considerations
The protocol was approved by the Research Committee of the Hospital Eva Perón.
the cardiac cycle. A balloon is inflated in the inferior vena cava to produce a transient occlusion, and 5 to 10 cardiac cycles at different preloads are recorded to obtain the end-systolic linear relationship, whose slope is Ees. (23) This parameter evaluates the contractile performance of the LV, independently of changes in preload or afterload. Non-invasive estimation of Ees can be obtained by Doppler echocardiography. The vascular component of VAC is estimated by Ea, which relates ESP (a parameter shared by the LV and the aorta) with SV, which depends on the elastic properties of the aorta, the peripheral resistance and the pulsatile component. (24) Ea increases when ESP increases or SV decreases, indicating in both cases increased vascular stiffness. “Pseudonormalization” of VAC may occur when concentric LV hypertrophy (which increases Ees) coexists with increased Ea, as seen in patients with hypertension and HF with preserved EF. Although VAC in AS has been evaluated with mathematical and experimental models, to our knowledge its relationship with the presence of symptoms or HF has not been established. Our study confirms what has been previously published about the lack of correlation between symptoms and stenosis severity or valvular load. We did not find significant differences among the three groups in AVA, although PG and MG were reduced in patients with AS HF, probably related with reduced SVI and EF. As expected, the E/E' ratio, a parameter of diastolic function, was higher in patients with AS HF, but there were no significant differences in the group with symptoms and without symptoms, suggesting that diastolic dysfunction does not correlate with the presence of symptoms. Ees was increased in patients with A AS, probably due to the previously mentioned concentric hypertrophy, and was normal in patients with AS HF and S AS. However, an important variation was observed in standard deviation values (coefficient of variation 57% and 48%, respectively), suggesting that in these groups contractility is decreased in some patients, by approximately 33%, according to a previous study performed in our laboratory. (25) In that study, we analyzed the relationship between ejectional parameters as EF, eFS and mFS and increased afterload, which would explain the reduction of these parameters in patients with AS HF and S AS, despite similar values of Ees. Ea was increased in patients with AS HF and S AS compared with A AS, with lower variation in Ees values (coefficient of variation 43% and 33%, respectively), indicating that vascular load was greater in these patients, probably related with the higher prevalence of cardiovascular risk factors which increase vascular stiffness. Ventricular-arterial coupling showed a progressive and significant reduction in the three groups, from the compensated stage of AS to the decompensated stage with HF, suggesting that the development of symptoms or HF are more related with the characteristics of vascular load than with those of valvular load. Antonini-Canterin et al. (26) were the first authors who published that patients with AS and hypertension developed symptomatics with larger AVA than patients without hypertension, postulating that the higher vascular load was responsible for the development of symptoms in these patients. In a subsequent study, Briand et al. (27) demonstrated an inverse correlation between reduced arterial distensibility and LV function. Rosca et al. (28) reported an inverse relation between aortic stiffness assessed by the aortic beta index and LV systolic function, and a positive correlation with diastolic dysfunction in patients with AS and preserved EF, independently of valvular load. Similar findings were published by Weisz et al. (29) in the evaluation of carotid stiffness in patients with moderate to severe AS. Aortic stiffness is not circumscribed to the ascending aorta, but also affects the descending aorta in patients with AS, as Petrini et al. (30) described in their paper using transesophageal echocardiography. Using aortic pulse wave velocity as an indicator of arterial stiffness, Kidher et al. (31) demonstrated that patients with higher aortic wave velocity (increased arterial stiffness) had worse quality of life before and after aortic valve replacement. Ramamurthi et al. (32) found that the prevalence of excessive vascular load was higher in patients with symptoms compared with those without symptoms. The presence of HF and exertional dyspnea related with arterial distensibility was analyzed by Kruszelnicka et al. (33) who demonstrated that decreased arterial distensibility affects exercise tolerance and correlates with HF, irrespective of AS severity. Park et al. (34) correlated symptoms with echocardiographic parameters in 498 patients, and reported that dyspnea was associated with LA dilation and diastolic dysfunction, syncope was associated with smaller LV dimension and angina was not related with any parameter in particular. Unlike our study, the authors included patients with preserved EF and did not analyze vascular load.

CONCLUSIONS

In severe aortic stenosis, VAC (Ea/Ees ratio) is increased in patients with symptoms or HF due to increased Ea and reduced Ees (particularly in patients with HF). The development of symptoms or HF in AS seems to be related with the characteristics of the vascular system, irrespective of AS severity.

Conflicts of interest

None declared. (See authors’ conflicts of interest forms in the website/Supplementary material).

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