Rosuvastatin Slows the Development of Diastolic Dysfunction in Calcific Aortic Stenosis

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Background and aim of the study: **The study aims were to test the effect of rosuvastatin on the progression of left ventricular (LV) diastolic function in patients with aortic stenosis (AS), and to evaluate the use of β-natriuretic-peptide (BNP) as a marker of diastolic dysfunction in this condition.**

Methods: **Sixty-one hypercholesterolemic, consecutive new referrals with moderate AS were administered rosuvastatin (Crestor™) 20 mg/day for 18 months, while a further 60 subjects with normal cholesterol levels remained untreated. The LV diastolic function was determined using conventional Doppler echocardiography, tissue Doppler imaging (TDI); BNP plasma levels were monitored when subjects entered the study and then assessed prospectively at six-month intervals until the study end.**

Results: **After an 18-month (mean 73 ± 24 weeks) period of treatment with rosuvastatin (Tx group), patients showed a significantly better diastolic function than untreated subjects (uTx group), as indicated by an isovolumic relaxation time (IVRT) (Tx 102.0 ± 42.8 versus 97.2 ± 19.1; p <0.001; uTx 99.7 ± 21.7 versus 95.2 ± 21.8 ms; p = 0.032), E/A ratio (Tx 1.0 ± 0.6 versus 0.9 ± 0.3, p = 0.52; uTx 1.2 ± 0.40 versus 0.9 ± 0.30 versus, p = 0.006), and E/E' ratio (Tx 11.4 ± 1.5 versus 11.4 ± 1.8, p = 0.19; uTx 15.4 ± 1.2 versus 12.3 ± 1.5, p <0.001). Similarly, at study end, plasma levels of BNP were significantly lower in the Tx group than in the uTx group [median (1st-3rd quartiles): 37.0 pg/ml (20.1-65.2 pg/ml) versus 57.1 pg/ml (46.9-98.2 pg/ml); p = 0.017].**

Conclusion: **The results of this prospective follow up study of asymptomatic patients showed that rosuvastatin treatment delays the progression of diastolic dysfunction in moderate AS when assessed using hemodynamic echocardiographic parameters or by the release of plasma physiological markers. Hence, the benefits of statin treatment in AS, which are known to affect the valve endothelium, also extend to changes affecting myocardial function itself.**

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After hypertension and coronary artery disease (CAD), aortic stenosis (AS) is the most prevalent form of cardiovascular disease in the Western world (1-3). It is usually caused by either the degenerative calcification of a trileaflet valve or the progressive stenosis of a congenital bicuspid valve (4). Calcific aortic valve disease is a progressive condition for which patients are usually referred to a tertiary care center at a late stage in the disease process (1,5,6).

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Although aortic valve calcification was once thought to be a passive process, recent insights into its pathogenesis have suggested an inflammatory process similar to that of atherosclerosis (7,8). While statins were considered first-line candidates for slowing the progress of AS (9), and despite promising results being obtained with animal models and retrospective studies (10-16) and also from one prospective non-randomized trial (13), the results of recent randomized clinical trials have failed to confirm the expected benefit (17-19). In fact, the suggestion that a lack of benefit from statins therapy in calcific AS may be due to the presence of extensive calcification indicates that early treatment with statins might be more beneficial.

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Impaired relaxation in AS patients as a consequence of left ventricular hypertrophy (LVH) has been demonstrated by Paulus and Brutsaert (20). Furthermore, a retrospective study conducted in a cohort of patients with different degrees of AS showed that rates of symptom progression and mortality were predicted by the presence of LVH, left atrial diameter and systolic function rather than the degree of outflow obstruction, as estimated by valvular pressure gradient. To date, no reports have described any relationship between AS progression and the development of diastolic dysfunction.

From a classic pathophysiologic perspective, the obstruction imposed on the left ventricle from the stenotic aortic valve produces systolic wall stress, which in turn (by applying La Place's law) leads to different left ventricular types because of the increased relative wall thickness. If a significant thickness occurs in the left ventricular septum and posterior wall, then an increased left ventricular mass may help to maintain the overall systolic function, despite an impairment in diastolic function arising.

Previously, the SEAS investigators (19) also demonstrated in asymptomatic patients with AS that associated structural changes such as LVH, mitral regurgitation, left ventricular end-diastolic volume and impaired filling pattern were independent predictors of the degree of AS, but not of its progression.

However, as statin therapy failed to prevent the progression of AS in multiple randomized controlled studies, including ASTRONOMER (18), SEAS (19) and SALTIRE (17), it is not unexpected that the degree of diastolic dysfunction continued to progress in the ASTRONOMER population. Moreover, it has been shown that diastolic parameters improve in both short- and long-term follow up after open surgical or percutaneous aortic valve replacement procedures. It is also plausible that, in the ASTRONOMER study, other contributing mechanisms to progressive diastolic dysfunction including underlying CAD may have affected the outcome.

To date, the few studies carried out to monitor plasma β-natriuretic-peptide (BNP) levels in patients with moderate to severe AS (21,22) have determined that an increased BNP level correlates with initial cardiac diastolic dysfunction.

Tissue Doppler imaging (TDI) is recognized as a non-invasive tool to determine abnormal relaxation, and has been shown to be effective in analyzing left ventricular diastolic function (23-25). In patients with different degrees of AS severity, TDI is effective in evaluating the diastolic dysfunction even in the absence of LVH (26-29). The use of TDI for the serial assessment of diastolic abnormalities in AS patients is not well known. In severe AS, both left atrial dilation and dysfunction have been shown to have adverse effects on the outcome. Typically, the left atrial size may serve as a surrogate marker of chronic diastolic function and left ventricular filling pressure (30).

The aim of the present study was to examine whether treatment with rosuvastatin improved diastolic abnormalities in AS patients, as evaluated by monitoring plasma BNP levels, left atrial volume and echocardiographic conventional and TDI diastolic parameters.

Clinical material and methods

Study population and entry protocol

Approval to conduct the study (IRB- 22352) was obtained from the Pedro Hispano Hospital Institutional Review Board, Matosinhos, Portugal, prior to study initiation. All study participants were fully informed and provided their signed consent prior to enrolment.

This open-label prospective study was conducted with asymptomatic patients with moderate AS, defined by an aortic valvular area (AVA) of 1.0-1.5 cm^2. The initial selection included 255 consecutive, statin-naive new AS patients who had been referred to the authors' in-patient and out-patient cardiology clinics for the Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) study to slow the progression of AS (13). Patients were excluded from the study if they had a history of CAD (myocardial infarction and/or angiographically demonstrated coronary artery stenosis), previous aortic valvular surgery, congenital cardiac disease (bicuspid aortic valve), previous statin therapy, active or chronic liver disease, or were currently receiving an angiotensin-converting enzyme inhibitor. No other medications were contraindicated, including other anti-hypertensive or oral hypoglycemic agents and insulin. Similarly, patients with echocardiographic evidence of rheumatic mitral valve disease, aortic regurgitation or a subaortic obstruction were excluded. Finally, a serum creatinine level ≥2.0 mg/dl was considered cause for exclusion, in order to minimize the risk of hypercalcemia as a potential confounding factor in these patients.

The application of exclusion criteria reduced the number of patients selected to 135; of these patients, 14 were unsuitable for study inclusion due to technical problems with their initial echocardiographic assessment, or to difficulties in obtaining details of their medical history. For all 121 participants, data were obtained on age, gender, smoking history, hypercholesterolemia, arterial hypertension (defined as average blood pressure >140/90 mmHg), and diabetes. At the

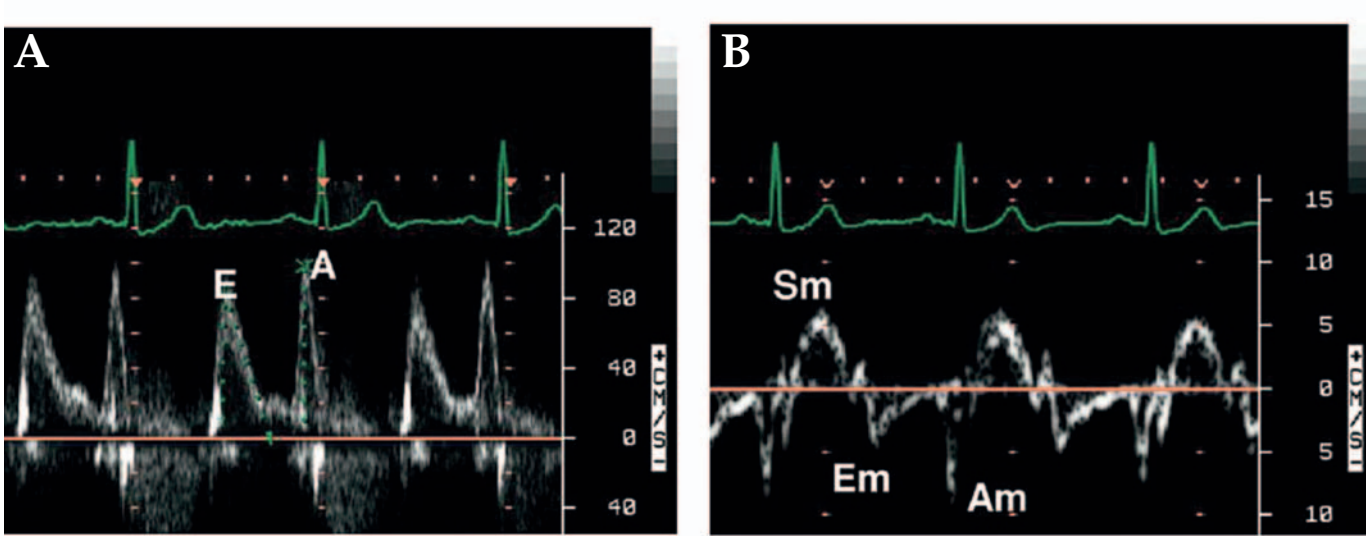

Figure 1: Representative mitral inflow and TDI diastolic parameters. A) Mitral inflow profile with measurement of peak early (E) and late (A) diastolic velocities in a patient with AS. In this case, an E/A ratio of 0.9 is derived. B) TDI tracing of mitral annulus with measurement of peak systolic (Sm), peak early diastolic (Em), and peak late diastolic (Am) annular velocities in the same patient as in panel (A).

onset of the study, all patients were without detectable evidence of inflammatory, neoplastic, metabolic or vascular disease on an initial history, examination or set of routine tests. All patients received standard clinical care throughout the study period.

Patients were analyzed on an intention to treat basis. During the course of the study, four rosuvastatin-treated (Tx) patients and three untreated (uTx) subjects withdrew their participation, five underwent valve replacement surgery (two Tx, three uTx), and one patient (Tx) died suddenly (no post-mortem analysis was carried out, at the family's request). In addition, four subjects in the uTx group died, two from sepsis and two from cancer.

Biochemical analyses

Blood samples were taken from patients after a 12-h fast. Samples for routine clinical biochemistry were processed in the clinical biochemistry laboratory of Pedro Hispano Hospital, following standard institutional protocols. An in-hospital audit had previously demonstrated sample result variabilities of between 5% and 15% for these assays (data not shown).

Blood samples for BNP monitoring were taken following a 10-min period of supine rest, immediately prior to echocardiography. Samples were drawn into chilled EDTA-containing tubes and immediately centrifuged at 4000 r.p.m. (4°C) for 15 min; the plasma was removed and stored at -70°C until taken for immunochemiluminometric analysis (BNP kit; Bayer Diagnostics, Tarrytown, NY, USA) or. The inter- and intra-assay variations were 5% and 4%, respectively.

Echocardiographic studies

Comprehensive transthoracic echocardiography was performed and reported at a single central laboratory (Acuson Sequoia C512 instrument; Siemens Healthcare, Erlangen, Germany) by one of two experienced cardiologists who sub-specialized in echocardiography (L.M. and I.B.). An immediate review allowed repetition of the study by the second cardiologist as needed to maintain quality control. Those investigators involved in performing the echocardiography and interpreting the echocardiograms were blinded to the patient treatment status. Hemodynamic progression was assessed using serial echocardiographic studies at six-month intervals.

Standard Doppler recordings were made of the left ventricular outflow tract and aortic valve from multiple views in order to obtain the peak transvalvular jet velocity (V_{max}), the mean and peak gradients, and AVA in accordance with international guidelines (21,31-34). The left atrial volume relative to body surface area was estimated from end-systolic measurements (23-27). Diastolic function was classified as described previously, using transmitral Doppler flow and TDI (Table I) (18,21,23,27,28,35).

Echocardiography was performed by two investigators, such that the reproducibility of their observations was assessed in a subset of 30 patients. The parameters examined demonstrated an intra-class coefficient correlation of between 0.962 and 0.989 (intra-observer) and 0.955 and 0.992 (inter-observer). Moreover, conventional Doppler and TDI parameters exhibited intra- and inter-observer coefficients of reproducibility of between 1.56 and 9.02. For intra-observer variability

Table I: Classification of diastolic dysfunction. Adapted from Refs. (24) and (25).

Stage	Name	Doppler transmitral parameters	Tissue Doppler imaging
I	Alteration of ventricular relaxation	E/A <0.8; E-DT 200 ms; E/E' ≤8	Septal E' <8
II	Pseudonormal	E/A 0.8-1.5; E-DT 160-200 ms; E/E' 9-12	Septal E' <8
III	Restrictive pattern	E/A >2; E-DT <150 ms; E/E' >13	Septal E' <8

E/A ratio: Peak values of E-wave and A-wave; E-DT: E-wave deceleration time; E/E': Average values of septal and lateral site; IVRT: Isovolumetric relaxation time.

(observer 1), the coefficients of variation and reproducibility were, respectively, 1.88% and 0.16 for E/A, and 3.89% and 0.18 for E/E'. For intra-observer variability (observer 2), the coefficients of variation and reproducibility were 2.01% and 0.14 m/s for transvalvular peak velocity (V_{max}) and 3.25% and 0.08 cm^2 for AVA, respectively. For inter-observer variability, the coefficients of variation and reproducibility were, respectively, 2.0% and 0.14 for E/A, and 2.91% and 0.14 for E/E'.

Statistical analysis

The patient characteristics were presented as mean ± SD if they were normally distributed continuous variables, while categorical variables were expressed as frequencies (percentage) and non-normally distributed continuous variables as median (1st-3rd interquartile ranges). Continuous variables were assessed using the Kolmogorov-Smirnov test with the Lilliefors correction (parameters: distribution unknown) to determine whether an assumption of normality was appropriate.

Reproducibility was assessed using the method of Bland and Altman (36,37), and expressed as a coefficient of reproducibility (twice the SD of the differences). The following statistical tests were used: group means were compared using a one-way ANOVA (normally distributed data) or the Mann-Whitney *U*-test (non-normally distributed data). The pre-study and follow up data were compared using the paired Student's *t*-test (normally distributed data) or the Wilcoxon test (non-normally distributed data). Chi-squared tests were used to assess differences in categorical variables. All statistical

Table II: Baseline clinical characteristics of the study population.

Characteristic	All patients	Rosuvastatin-treated	Untreated	p-value
Clinical data				
Age (years)+	73.7 ± 8.9	73.4 ± 8.5	73.9 ± 9.4	0.749
Male gender (%)	47	34	60	0.006**
BMI (kg/m^2)	28.5 ± 4.7	28.9 ± 4.5	28.3 ± 5.0	0.570
Arterial hypertension (%)	64	74	53	0.024*
DBP (mmHg)+	75.9 ± 12.9	73.4 ± 13.6	78.4 ± 13.6	0.033*
SBP (mmHg)+	150.6 ± 22.9	146.6 ± 26.2	154.4 ± 18.6	0.060
Diabetes mellitus (%)	32	43	22	0.019*
Sinus rhythm (%)	88	92	83	0.179
Heart rate (beats/min)+	72.8 ± 13.0	73.8 ± 13.1	71.8 ± 12.8	0.379
Biochemical data				
Total cholesterol (mg/dl)+	217.7 ± 50.1	243.0 ± 40.5	192.0 ± 45.8	<0.001**
HDL (mg/dl)+	54.0 ± 12.7	55.0 ± 13.2	53.1 ± 12.2	0.399
LDL (mg/dl)+	137.5 ± 39.6	158.2 ± 31.7	116.5 ± 20.9	<0.001**
BNP (pg/ml)#	40.0 (18.9-90.5)	34.7 (15.5-83.4)	47.0 (24.6-91.6)	0.095

+Values are mean ± SD.
#Values are median (interquartile range).
*, p <0.05; **, p <0.005 between compared groups.
BMI: Body mass index; BNP: β-Natriuretic-peptide; DBP: Diastolic blood pressure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SBP: Systolic blood pressure.

Table III: Basal echocardiographic characteristics of the study population.

Characteristic	All patients	Rosuvastatin-treated	Untreated	p-value
Echocardiography				
Peak jet velocity (m/s)	3.63 ± 0.62	3.65 ± 0.64	3.62 ± 0.61	0.79
Aortic valve area (cm^2)	1.21 ± 0.38	1.23 ± 0.42	1.20 ± 0.35	0.64
End-diastolic long-axis diameter (mm)	51.7 ± 5.1	50.1 ± 5.8	52.5 ± 4.1	0.11
End-systolic long-axis diameter (mm)	33.9 ± 4.4	33.2 ± 4.9	34.6 ± 3.8	0.07
Ejection fraction (%)	54.9 ± 3.1	54.3 ± 2.1	55.6 ± 4.4	0.06
Left ventricular mass index (g/m^2)	84.9 ± 23.6	81.9 ± 29.1	87.5 ± 20.2	0.09
Left atrial volume index (ml/m^2)	36.4 ± 11.4	36.3 ± 10.4	35.9 ± 11.7	0.62
Conventional diastolic parameters				
E-wave DT (ms)	279.6 ± 99.7	293.9 ± 133.2	274.8 ± 78.2	0.73
IVRT (ms)	98.6 ± 20.7	97.2 ± 19.1	95.2 ± 21.8	0.42
E/A ratio	0.9 ± 0.4	0.9 ± 0.3	0.9 ± 0.4	0.57
Tissue Doppler imaging				
E′ velocity (cm/s)	5.5 ± 1.0	5.9 ± 1.0	5.6 ± 1.0	0.39
A′ velocity (cm/s)	10.1 ± 2.9	10.3 ± 2.9	9.9 ± 2.1	0.21
S′ velocity (cm/s)	8.4 ± 2.9	8.0 ± 2.1	8.7 ± 2.0	0.23
E/E′	11.9 ± 1.9	11.4 ± 1.8	12.3 ± 1.5	0.07

Values are mean ± SD.
DT: Deceleration time; IVRT: Isovolumic relaxation time.

analysis was performed using SPSS for Windows software (version 17.0.1; SPSS Inc., Chicago, IL, USA). Two-tailed p-values <0.05 were considered to be indicative of statistical significance.

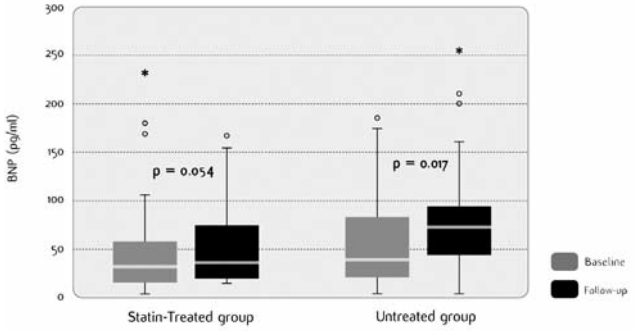

*Figure 2: Effect of rosuvastatin on serum BNP levels. Box-whisker plots are shown with boxes indicating first, second, and third quartiles. The small circle point dots are data points, and the column denotes the data mean M (vertical bar indicates SD). The SD error bars include about two-thirds of the sample, and 2 SD error bars would encompass approximately 95% of the sample. *, p <0.05.*

Results

Study population

The patient groups were selected from consecutive referrals to the authors' cardiology clinic on the basis of their plasma LDL-cholesterol levels. A detailed breakdown of the social and clinical differences between the groups has been reported elsewhere (13), and a summary is provided in Table II. In addition to lipid levels, the patient groups also varied with respect to male gender (Tx 34% versus uTx 60%, p = 0.006), while the presence of two commonly associated cardiovascular risk variables, namely arterial hypertension (Tx 74% versus uTx 53%, p = 0.024) and diabetes mellitus (Tx 43% versus uTx 22%, p = 0.019), was more common in the rosuvastatin-treated group.

Baseline cardiac function

At study entry, both groups had a similar and normal left ventricular systolic function (Table III), as indicated by the ejection fraction (Tx 54.3 ± 2.1%; uTx 55.6 ± 4.4%; p = 0.160), end-diastolic long-axis diameter (Tx 50.1 ± 5.8 mm; uTx 52.5 ± 4.1 mm; p = 0.11), and end-systolic long-axis diameter (Tx 33.2 ± 4.9 mm; uTx 34.6 ± 3.8 mm; p = 0.07). Furthermore, there were no significant differences in left ventricular diastolic function as assessed by standard Doppler measurements,

Table IV: Comparison of echocardiographic findings in rosuvastatin-treated and untreated groups at baseline and after follow up.

Parameter	Rosuvastatin-treated			Untreated		
	Baseline	Follow up	p-value	Baseline	Follow up	p-value
Echocardiography						
Peak jet velocity (m/s)	3.56 ± 0.56	3.86 ± 0.62	<0.001*	3.64 ± 0.65	3.73 ± 0.74	0.112*
Aortic valve area (cm^2)	1.24 ± 0.35	1.11 ± 0.35	<0.001*	1.22 ± 0.40	1.16 ± 0.42	0.010*
End-diastolic short-axis diameter (mm)	52.6 ± 4.2	53.9 ± 2.6	0.005*	50.1 ± 7.1	53.7 ± 5.0	<0.001*
End-systolic short-axis diameter (mm)	34.1 ± 4.0	35.7 ± 2.3	0.008*	33.2 ± 5.3	35.1 ± 3.3	0.010*
Left ventricular mass index (g/m^2)	81.9 ± 29.1	84.2 ± 19.2	0.53	87.5 ± 20.2	85.6 ± 15.9	0.46
Left atrial volume index (ml/m^2)	36.3 ± 10.4	38.2 ± 10.5	0.09	35.9 ± 11.7	39.1 ± 12.5	0.004*
Conventional diastolic parameters						
E-wave DT (ms)	274.8 ± 78.2	321.1 ± 143.2	0.040*	293.9 ± 133.2	280.2 ± 115.6	0.44
IVRT (ms)	97.2 ± 19.1	102.0 ± 42.8	<0.001*	95.2 ± 21.8	99.7 ± 21.7	<0.032
E/A ratio	0.9 ± 0.3	1.00 ± 0.6	0.52	0.9 ± 0.4	1.2 ± 0.4	0.006*
Tissue Doppler imaging						
E′ velocity (cm/s)	5.9 ± 1.0	7.4 ± 1.1	0.27	5.6 ± 2.0	5.2 ± 1.6	0.19
A′ velocity (cm/s)	10.3 ± 2.9	9.6 ± 3.0	0.32	9.9 ± 2.1	9.6 ± 2.3	0.13
S′ velocity (cm/s)	8.0 ± 2.1	8.2 ± 2.6	0.92	8.7 ± 2.7	9.9 ± 3.0	0.03
E/E′	11.4 ± 1.8	11.4 ± 1.5	0.19	12.3 ± 1.5	15.4 ± 1.2	<0.001

Values are mean ± SD.
*, p <0.05 between compared groups.
Abbreviations as Table III.

with both groups showing type 1 diastolic dysfunction: E/A ratio (Tx 0.9 ± 0.3; uTx 0.9 ± 0.4; p = 0.57); E-wave deceleration time (DT) (Tx 293.9 ± 133.2 ms; uTx 274.8 ± 78.2 ms; p = 0.73); IVRT (Tx 97.2 ± 19.1 ms; uTx 95.2 ± 21.8 ms; p = 0.42), or by tissue Doppler imaging [E′ (Tx 5.9 ± 1.0 cm/s; uTx 5.6 ± 1.0 cm/s; p = 0.39); A′ (Tx 10.3 ± 2.9 cm/s; uTx 9.9 ± 2.1 cm/s; p = 0.21); and E/E′ (average values of septal and lateral site) ratio (Tx 11.4 ± 1.8; uTx 12.3 ± 1.5; p = 0.07).

Parameters of aortic stenosis

Previously obtained data from the present cohort of patients confirmed that rosuvastatin treatment slowed the progression of AS with regards to the AVA and peak jet velocity (9) (Table IV).

Rosuvastatin treatment and left ventricular function

During the study there was no evidence for any change in left ventricular mass in either rosuvastatin-treated (p = 0.532) or non-treated (p = 0.458) patients.

After a mean follow up of 73 ± 24 weeks, a generalized and statistically significant increase in diastolic dysfunction was observed in untreated patients (E/A ratio 0.9 ± 0.4 versus 1.2 ± 0.4, p = 0.006; DT 293.9 ± 133.2 ms versus 280.2 ± 115.6 ms, p = 0.44; IVRT 95.2 ± 21.8 ms versus 99.7 ± 21.7 ms, p <0.032) which was not seen in the rosuvastatin-treated group [E/A ratio 0.9 ± 0.3 versus 1.0 ± 0.6, p = 0.52; DT 274.8 ± 78.2 ms versus 321.9 ± 143.2 ms, p = 0.040; IVRT 97.2 ± 19.1 versus 102.0 ± 42.8 ms, p <0.001].

This increase in the Doppler echocardiography markers of diastolic dysfunction was also seen in TDI markers of diastolic dysfunction. Hence, in untreated patients there was a statistically significant increase in the E/E′ mitral ratio during follow up when compared to the rosuvastatin-treated group (E/E′ 15.4 ± 1.2 versus 11.4 ± 1.5, p <0.001).

In summary, the untreated population developed type II or pseudonormal diastolic dysfunction during the course of the study [E/A ratio 1.2 ± 0.4, E-wave DT 280.2 ± 115.6 ms; IVRT = 99.7 ± 21.7 ms; E′ 5.2 ± 1.6 cm/s]. However, in the rosuvastatin group the patients did not progress from the type I diastolic dysfunction they exhibited at the start of the study [E/A ratio 0.9 ± 0.3; E-wave DT 274.8 ± 78.2 ms; IVRT 97.2 ± 19.1 ms; E′ 5.9 ± 1.0 cm/s]. In the untreated group, 48 patients (80%) had deteriorated from type I to type II diastolic dysfunction by the end of the study period, whereas in the rosuvastatin-treated group only five patients (8.2%; p <0.0001) showed such deterioration (Fig. 1).

Left atrial chamber size

At baseline, there was no significant difference between groups in terms of indexed left atrial volume (uTx 35.9 ± 11.7 ml/m^2 versus Tx 36.3 ± 10.4 ml/m^2; p = 0.619). However, at the end of follow up, values in untreated subjects had increased significantly more than in rosuvastatin-treated patients (uTx 35.9 ± 11.7 ml/m^2 versus 39.1 ± 12.5 ml/m^2, p = 0.004; Tx 36.3 ± 10.4 ml/m^2 versus 38.2 ± 10.5 ml/m^2, p = 0.094) (Table IV).

β Natriuretic peptide

At the start of the study, serum BNP levels were similar in both groups (Tx 34.7 pg/ml (15.5-83.4); uTx 47.0 pg/ml (24.6-91.6); p = 0.095). However, at the end of the follow up period, although BNP serum levels remained essentially unchanged in the rosuvastatin-treated group (37.0 pg/ml; 20.1-65.2), they had increased significantly in the untreated group (57.1 pg/ml; 46.9-98.2; p = 0.017) (Fig. 2).

Correlation between AS progression and diastolic dysfunction

In the RAAVE study (13), an evaluation was made of the independent association between E/E ratio as a diastolic function marker and the progression of AS using a multivariate logistic regression analysis, having adjusted the model for predictors such as baseline AVA and V_{max}, gender, age, hypertension, diabetes mellitus, LDL-cholesterol, degree of valve calcification, LVH, mitral regurgitation, left ventricular end-diastolic volume, statin use, AS basal severity, and impaired filling pattern. The variable progression of AS was considered as a variable or independent outcome, and classified according to the criteria presented above. From this analysis, it was concluded that E/E' is not an independent predictor of AS progression [odds ratio (OR) 1.00, 95% confidence interval (CI) 0.99-1.10, p = 0.96]. Rather, the only independent predictor of AS progression was statin therapy (OR 0.42, 95% CI 0.16-1.10, p = 0.078). In a multiple linear regression analysis in a model adjusted for these covariates, statin therapy remained the only independent predictor of disease progression.

Discussion

The results of this observational, prospective, non-randomized trial have shown that lipid-lowering therapy improves cardiac diastolic function in AS patients after a median follow up of 1.5 years.

Since 1990, new imaging modalities such as tissue Doppler imaging, color M-mode Doppler and magnetic resonance imaging have improved the understanding of diastolic function. Over the past 10 years, new techniques and indices for assessing diastolic function have continued to evolve, while recent epidemiological studies have demonstrated that diastolic heart failure is increasing in prevalence. Fortunately, during the past five years there has been a shift from the research level, to the development of diagnostic techniques, to clinical trials to establish targeted treatment for patients with diastolic heart failure.

The slowdown of diastolic dysfunction with statin treatment cannot be 'captured' with a single physiologic parameter; rather, a combination of parameters and findings should be used. The results of the present study emphasize the importance of echocardiographic guiding therapy (wide availability, low cost, and easy access), and also the importance of statins effects that go beyond pure lipid-lowering mechanisms.

Future research into diastole will be required to establish the factors that promote the transition from preclinical to a clinically overt disease, the value of new drugs (including endothelial receptor antagonists), and the glucose cross-link breakers that can help to determine whether different degrees of diastolic dysfunction at baseline should be treated in different ways. Furthermore, additional and simpler ways to identify left ventricular diastolic dysfunction at the earliest and most treatable stages are needed, as well as load-independent indices of left ventricular diastolic filling, in particular in patients with atrial fibrillation.

It has been suggested that statins may have beneficial effects on diastolic parameters, predominantly by attenuating the degree of LVH and cardiac fibrosis in murine models of hypertension (38,39).

Several clinical studies have been conducted to evaluate AS progression and diastolic dysfunction in patients with varying degrees of AS severity (26,27,29,40). Interesting differences have been identified between the RAAVE study (13) and other trials. In RAAVE, as in animal and retrospective clinical studies, statins were used in the setting of hypercholesterolemia, whereas the randomized trials systematically excluded patients with hypercholesterolemia. This variance may help to explain the positive RAAVE findings.

In contrast, whereas the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) study (17) might have been too small, with a too-short follow up, and included individuals with AS that was too advanced to show any beneficial effects, two larger trials - SEAS (19) and ASTRONOMER (18), both of which were designed to include a large sample - had a much longer follow up and enrolled patients with mild to moderate AS; they also failed to show any benefits from the statins treatment, despite large reductions in LDL-cholesterol levels. It is possible that the similari-

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ties in the role of the lipid hypothesis in atherosclerosis and AS may lie in the initiation stage, and that AS disease progression may depend on other factors.

Previously, the ASTRONOMER group demonstrated, in mild and moderate AS, that measures of diastolic function were abnormal and related to the increased severity of AS (26). A SEAS substudy has already shown that the left ventricular diastolic function was impaired, as was evident from the increased left ventricular filling pressures (measured by septal E/E' and E/Vp) and impaired left ventricular relaxation (measured by reduced septal E') (27). Bruch et al. (28) have previously demonstrated an impairment in diastolic function by using TDI in symptomatic patients with advanced AS and LVH, and showed the E/E' ratio to allow for a reliable and reproducible estimation of left ventricular filling pressures in AS patients. Despite a lack of clinical studies examining the effect of statins in preventing diastolic dysfunction in AS patients, the results of a study conducted by Fukuta et al. (41) suggested that statin therapy - due to its pleiotropic effects - may lower mortality in patients with diastolic heart failure. The ASTRONOMER substudy has shown that statin therapy did not affect the progression of diastolic function, mainly because the echocardiographic analysis was limited (the study was designed to evaluate only the statins effects on AS progression rather than to analyze the diastolic progression).

The augmented left atrial-left ventricular pressure gradient during early diastole is a consequence of an ameliorated left ventricular relaxation in response to slow afterload progress in the statins group due to slow AVA progression, and probably to their pleiotropic effects in LVH. As a result, the E/A ratio did not show a worsening diastolic dysfunction. The E-wave DT also did not decrease in the treated group, demonstrating a slower progressive left ventricular stiffness and the unchanged status of relaxation and compliance due to a slower left ventricular end-diastolic pressure progression. Accordingly, the results of IVRT measurements in the rosuvastatin group suggested beneficial treatment effects in left atrial pressure and volume.

As in other reports, the present study showed no decrease in systolic S'-wave velocity (TDI); hence, it was concluded that there was no significant subclinical deterioration of the left ventricular systolic function.

At the same time, it should be emphasized that the present study population clearly had no other contributing factors or mechanisms of progressive diastolic dysfunction, such as underlying CAD, that could affect the results and the outcome of these patient populations.

The results of the present study also showed that statins can decrease serum BNP levels, though the exact mechanism and clinical implications remain to be elucidated and further research using larger studies is needed to confirm these findings. However, high serum BNP levels may also be caused by structural myocardial changes occurring early in the natural history of AS, as well as by an initial left ventricular dysfunction that is not detectable by imaging techniques such as conventional two-dimensional echocardiography.

By inhibiting cardiac fibrosis, statins may have beneficial effects and could improve myocardial function. Furthermore, treatment with statins significantly reduced the collagen volume fraction in the non-ischemic regions. Indeed, a detailed assay confirmed that simvastatin treatment could also inhibit the expression of collagen I at both mRNA and protein levels (42).

Myocardial fibrosis has been reported as the most powerful predictor of serum BNP values, and BNP has been shown to possess anti-fibrotic properties. Aside from the role of atrial and/or ventricular myocardial wall stretch and stress, the influence of structural heart disease has not been discussed. Although patients with myocardial fibrosis had three-fold higher serum BNP values, this association was not sufficiently robust to serve as an independent predictor of BNP concentration.

In *conclusion*, the results of the present study showed that, under statin therapy, left atrial size and volume are preserved in AS patients, which in turn helps to maintain optimal cardiac output and left ventricular end-diastolic pressure and slow the severity of valve stenosis and impaired left ventricular compliance. Consequently, statin treatment can prevent clinical deterioration and the occurrence of atrial fibrillation, thus altering the spontaneous outcome (3).

The pleiotropic effects of statins emphasize the beneficial effects of statins, independent of their LDL-lowering abilities, and may provide insight into potential mechanisms involved in the improved survival of diastolic heart failure patients. Such pleiotropic effects include an improved microvascular circulation and endothelial function through up-regulated nitric oxide synthase, the attenuation of cardiac remodeling by reducing ventricular hypertrophy secondary to hypertension and angiotensin II, a down-regulation of angiotensin I receptors, and a decreased secretion of matrix metalloproteinases (44,45).

The major clinical implications and value of the present study have been to prove, by adequate and accurate methodology in a non-randomized prospective study, that statin therapy slows the progression of left

ventricular diastolic dysfunction as assessed by echocardiographic parameters and serum BNP levels.

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