BASIC SCIENCES

Rosuvastatin Slows the Progression of Aortic Stenosis Caused by Hypertension Regardless of Its Lipid-Lowering Effects

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SUMMARY

Background
There is epidemiological evidence associating cardiovascular risk factors with aortic valve stenosis. The development of aortic valve stenosis has been recently demonstrated in a hypertensive animal model. We hypothesize that treatment with rosuvastatin modifies this transformation.

Objective
To evaluate the effect of rosuvastatin on the development of aortic valve stenosis.

Material and Methods
Hypertension was induced in 43 male NZ rabbits by a one-kidney, one-clip Goldblatt procedure. The animals were randomly assigned to 3 groups: HT (n=17) without treatment; HT+R (n=14) treated with rosuvastatin 2.5 mg/kg/day and HT+R+C (n=12) treated with rosuvastatin 2.5 mg/kg/day + cholesterol-enriched diet to keep baseline cholesterol levels. A control group (CG) underwent sham surgery (n=15). The characteristics of the aortic valve were measured by echocardiography at baseline, 3 and 6 months after inducing hypertension.

Results
After 6 months of follow-up, SBP and DBP presented greater increase in the group HT (49% and 40%, respectively; $p < 0.001$) compared to groups treated with rosuvastatin (SBP = 23% and 25%; DBP = 28% and 26%; $p < 0.001$ for HT+R and HT+R+C, respectively). Total cholesterol decreased by 45.7% ($p < 0.01$) only in HT+R group. The aortic valve became thickened in the HT group (0.50 ± 0.01 vs. 0.62 ± 0.02 mm; $p < 0.01$); there were no significant differences in HT+R and HT+R+C. Finally, the aortic valve area was reduced in HT (0.277 ± 0.024 vs. 0.208 ± 0.014 cm2; $p < 0.05$), had no differences in HT+R and HT+R+C, and presented a non-significant increase in CG (0.264 ± 0.022 vs. 0.32 ± 0.016 cm2; p=0.07).

Conclusions
Rosuvastatin slows the progression of aortic valve stenosis caused by hypertension. This protection might be independent of the lipid-lowering effect of the drug.

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Key words > Statins - Aortic Valve Stenosis - Hypertension - Dyslipemia - Pleiotropic Effects

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Abbreviations >

AVA	Aortic valve area	**HT+R+C**	Hypertension + Rosuvastatin + Cholesterol group
AS	Aortic stenosis	**H**	Hypertension
CG	Control group	**oxLDL**	Oxidized low-density lipoprotein
cGMP	Cyclic guanosine monophosphate	**LOX-1**	Lectin-like oxidized LDL receptor
HDL-C	High density lipoprotein-cholesterol	**NO**	Nitric oxide
HMG CoA	3-hydroxy-3-methylglutaryl-coenzyme A	**SBP**	Systolic blood pressure
HTG	Hypertension group	**SOD**	Superoxide dismutase
HT+R	Hypertension + Rosuvastatin group	**LV**	Left ventricle
DBP	Diastolic blood pressure		

BACKGROUND

Aortic stenosis (AS) is the most common acquired valvular heart disease in adults and is the second most common condition requiring cardiovascular surgery. (1, 2) Despite the high prevalence of AS, most of the pathophysiological mechanisms still remain unclear. Several atherosclerosis risk factors have been associated with the development and progression of AS: age, smoking habits, high cholesterol levels, low high density lipoprotein-cholesterol (HDL-C) levels, hypertension (HT), high lipoprotein (a) levels and diabetes. (3-10) In this sense, our group has demonstrated the development of AS in an experimental model of normocholesterolemic hypertension, showing a direct association between the development of AS with high blood pressure levels. (11) Subsequent studies have shown increased oxidative stress with greater superoxide dismutase (SOD) activity and expression, increased tissue nitrotyrosine and reduction in tissue cGMP. Plasma levels of oxidized low-density lipoprotein (oxLDL) also increase. (12) Previous histological studies have demonstrated that lipid and oxidized lipoprotein depositions in the leaflets occur early in the development and progression of AS. (13. 14) Probably increased oxidative stress and other atherosclerotic stimuli due to HT may be responsible for the development of the aortic valve disease.

HMG-CoA reductase inhibitors, also known as statins, are efficient lipid-lowering agents in preventing cardiovascular events. (15, 16) In addition, these drugs have antioxidant and anti-inflammatory properties independent of their lipid-lowering effects. (17) However, recent clinical trials evaluating the use of statins in AS have not demonstrated a significant benefit; therefore, the indication of these agents in AS is controversial. (18-20) These trials have been conducted on patients with different degrees of severity of the disease; thus, it is difficult to establish if these drugs play any role in the prevention of early valve damage.

The hypothesis of this study is that rosuvastatin might reduce the deleterious impact of HT on the aortic valve and that this protective effect would be independent of its lipid-lowering effect.

MATERIAL AND METHODS

Model of hypertension

Hypertension was induced in 43 male New Zealand rabbits by a one-kidney, one-clip Goldblatt procedure. (21) Direct blood pressure measurements were obtained once a week from all animals through catheterization of the central ear artery. Hypertension was defined as blood pressure levels two standard deviations higher than the average preoperative values during two consecutive weeks. Cutoff values were 114 mm Hg for systolic blood pressure (SBP) and 88 mm Hg for diastolic blood pressure (DBP). Hypertensive animals were randomly assigned to one of the following groups: HTG (n = 17), fed a regular diet; HT+R (n = 14) , regular diet + rosuvastatin 2.5 mg/kg/day in the drinking water and HT+R+C (n = 12) regular diet + rosuvastatin 2.5 mg/kg/day in the drinking water + cholesterol-enriched diet to keep normal cholesterol levels. Cholesterol supplementation started with a concentration of 0.04% which was modified according to plasma cholesterol levels measured every two weeks in each animal. A control group (CG) underwent sham surgery (n = 15). Animals were treated according to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health.

Echocardiography

Transthoracic echocardiography was performed by applying standard practice guidelines at baseline, 3 and 6 months. Animals were sedated with an intramuscular injection of ketamine (20 mg/kg) and xilazine (1 mg/kg). Ultrasound images were obtained with a 12-MHz phased-array probe connected to a Sonos 5500 ultrasound scanner (Philips Medical Imaging, Andover, Massachusetts). A parasternal short-axis view at the mid left ventricular (LV) level was used to measure the following parameters: LV end-systolic and end-diastolic dimensions, interventricular septum and LV posterior wall thickness. The LV mass was calculated using the modified Devereux formula. (22) Peak and mean flow velocities across the aortic valve were determined using continuous-wave Doppler echocardiography by systematically sampling the flow from different acoustic windows and averaging the values for four to five beats. The maximal instantaneous gradient across the aortic valve and the mean gradient were derived from aortic Doppler velocities by the Bernoulli equation. The aortic valve area (AVA) was measured by the continuity equation. (23) The investigator who measured the echocardiographic parameters was blind to the treatment allocation of each animal.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation . Student's t test was used to analyze the differences between SBP and DBP at baseline and at the moment of randomization. Intragroup changes between the parameters measured during the follow-up period were evaluated using one-way repeated measures analysis of variance (ANOVA). Levene test was used to confirm the homogeneity of variances and Mauchly's sphericity test to determine if the assumption of sphericity had been violated. Intergroup comparisons were done with one-way ANOVA. Intragroup and intergroup differences were individualized using the post hoc Sidak and Student-Newman-Keuls tests, respectively. A p value < 0.05 was considered statistically significant.

RESULTS

Blood pressure and plasma cholesterol levels

Baseline SBP and DBP values were 101.3 ± 1 mm Hg and 78.6 ± 0.8 mm Hg, respectively, and increased significantly at the moment of randomization (127.4 ± 2.2 mm Hg; p < 0.001 and 96 ± 1.9 mm Hg; p < 0.001). After 6 months of follow-up, the highest increase in SBP and DBP was seen in the HTG compared to baseline values (49% and 40%, respectively; p < 0.001). Both parameters also showed a significant increase in the groups HT+R and HT+R+C (SBP 23% and 25%; DBP 28% and 26%, respectively; p < 0.001); however, this increase was lower compared to that of the HTG (Figures 1 and 2).

Figure 3 shows total cholesterol levels during follow-up. Baseline cholesterol level was 48.8 ± 2.3 mg/dl. In the HT+R group, cholesterol level decreased significantly 2 weeks after initiating treatment (38.3 ± 4 mg/dl; p < 0.05). The maximum lipid-lowering effect occurred at week 8 at remained stable, reaching a reduction of 45.7% (p < 0.01)in the group HT+R at the end of the study.

Echocardiographic evaluation of aortic valve stenosis progression

Table 1 shows the echocardiographic parameters studied. There was a nonsignificant increase in LV mass in groups HTG, HT+R and HT+R+C over the study period. The analysis of LV mass index (LVMI) was determined in each animal by body weight and revealed a significant increase only in the HTG during echocardiographic evaluation at 6 months.

Animals in CG, HT+R and HT+R+C groups did not show significant differences in leaflet thickness throughout the study, while those in the HTG had a progressive and significant increase (baseline: 0.50 ± 0.02 mm; 3 months: 0.58 ± 0.02 mm, p < 0.05 vs. baseline; 6 months: 0.62 ± 0.02 mm, p < 0.005 vs. baseline).

Finally, as shown in Figure 4, AVA showed a significant reduction in the HTG at 3 months (0.200 ± 0.029 cm2; p < 0.05) and 6 months (0.208 ± 0.014 cm2; p < 0.05) compared to baseline values (0.277 ± 0.024 cm2). Conversely, animals in HT+R and HT+R+C groups did not show significant differences in AVA during the study, while those in CG presented a significant increase at 6 months (baseline: 0.264 ± 0.022 vs. 6 months: 0.32 ± 0.016 cm2; p = 0.07). As shown in Table 1, peak aortic valve gradient increased significantly only in the HTG at 3 months (baseline: 9.8 ± 1.3 mm Hg vs. 3 months: 20.5 ± 3.6 mm Hg; p < 0.05) and at 6 months (21.2 ± 3.4 mm Hg; p < 0.05).

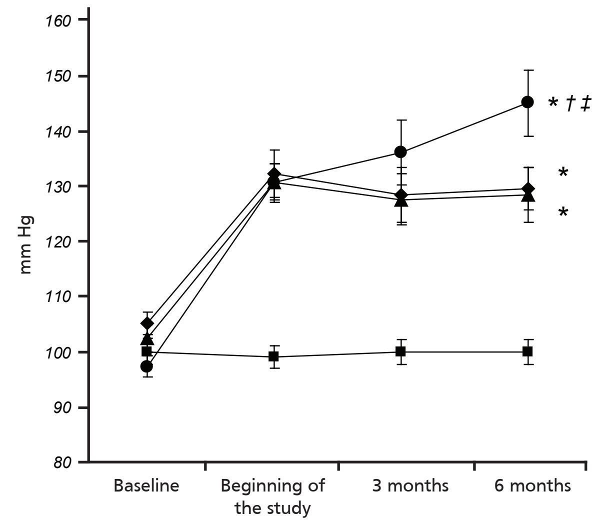

Fig. 1. Systolic blood pressure during the study. (■) CG, (●) HT group, (•) HT+R group and (▲) HT+R+C group. * p < 0.001 vs. CG; † p < 0.05 vs. HT-R; ‡ p < 0.05 vs. HT-R-C.

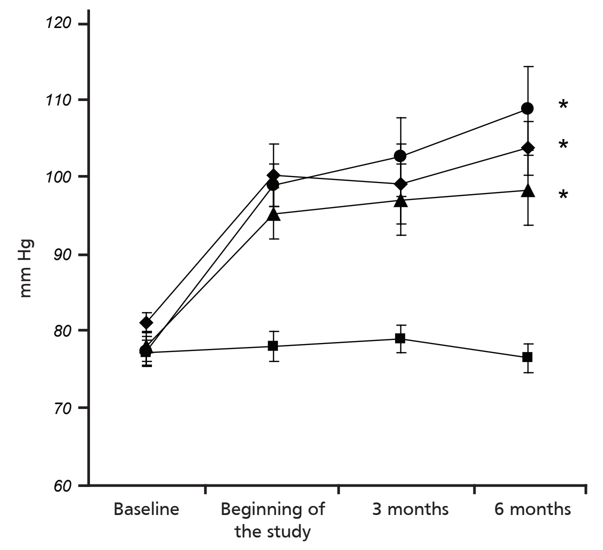

Fig. 2. Diastolic blood pressure during the study. (■) CG, (●) HT group, (•) HT+R group and (▲) HT+R+C group. * p < 0.001 vs. CG.

DISCUSSION

The prevalence of AVS is high, being the leading cause of acquired heart valvular disease in adults. (1, 2) Progression of AS is associated with morbidity and mortality, thus many patients undergo aortic valve replacement. (24) For this reason there is an increasing interest in elucidating the mechanisms related with the development and evolution of the disease and in finding the therapeutic tools to delay its progression. The main result of the present study is that treatment with rosuvastatin attenuated the development of AS in an experimental model of hypertension independently of changes in plasma cholesterol levels.

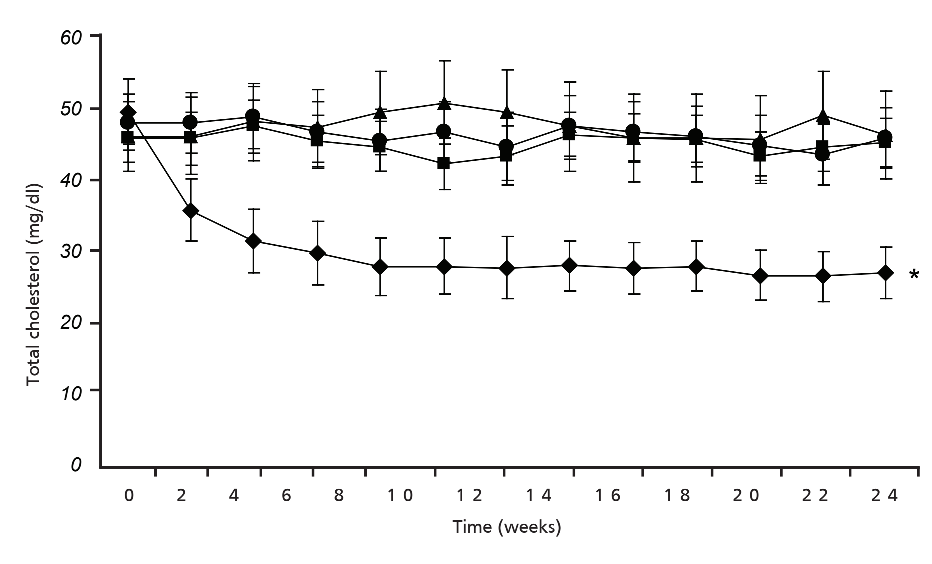

Fig. 3. Total cholesterol concentration by group during 6-month follow-up. (■) CG, (●) HT group, (•) HT+R group and (▲) HT+R+C group. * $p < 0.001$ vs. GC.

For several years, AS was considered a passive degenerative process of the aortic valve; however, it has come to be recognized as an active process sharing many clinical and histological features with atherosclerosis. (13) In fact, several studies have demonstrated an association between conventional risk factors for atheromatosis and greater risk for the development and progression of AS. (3-10) The histological features of the disease include lipoprotein deposition, chronic inflammation and tissue remodeling. (13) A recent study has reported the presence of oxLDL in the leaflets of patients with AS and has shown a correlation between these oxidized lipids, inflammation and the degree of leaflet calcification. (25)

Of interest, a considerable proportion of patients with AS have normal plasma cholesterol levels, suggesting that other factors must be related with the development of the disease. (9, 19)The importance of HT in this process has been highlighted by few epidemiological studies. (26, 27) Based on the hypothesis that HT per se might produce AS, our group has previously demonstrated that induction of experimental chronic HT reduces the AVA, increases peak and mean aortic gradient and produces thickening of the aortic valve leaflets after 4 months of follow-up. (11) The oxidative profile associated with HT (12) showed: 1) reduction in the SOD activity, one of the main components of the antioxidant defense mechanism, 2) increased tissue nitrotyrosine, indirectly reflecting sequestration of nitric oxide (NO), 3) reduced cGMP, a secondary mediator of NO action, and, 4) increased plasma levels of oxLDL. Although these preclinical results occurred with normal cholesterol levels, the pathophysiological role of plasma lipid levels in this state of high oxidative stress should not be ruled out. In fact, HT increases infiltration of macromolecules, proteins and lipoproteins through the endothelial barrier (28) increasing vascular sensitivity even with physiological levels of atherogenic plasma lipids. In consequence, we speculate about the possibility that plasma lipids are a risk factor for the development of AS, even within normal concentrations. Thus, it is interesting to evaluate the impact of a statin on the development of AS in HT and normal cholesterol levels. The present study shows that rosuvastatin reduces the progression of AS after 6 months of exposure to experimental HT, demonstrating that the drug attenuates AVA decrease while the control group presents a non-significant increase in the AVA attributed to animals' growth. Similar benefits are observed in leaflet thickening. These findings are present in both rosuvastatin groups; therefore, the protective effect achieved on the aortic valve might be different from the lipid-lowering effect.

Most pharmacological agents are designed for a specific action; however, in some cases it is possible to identify actions other than those for which the

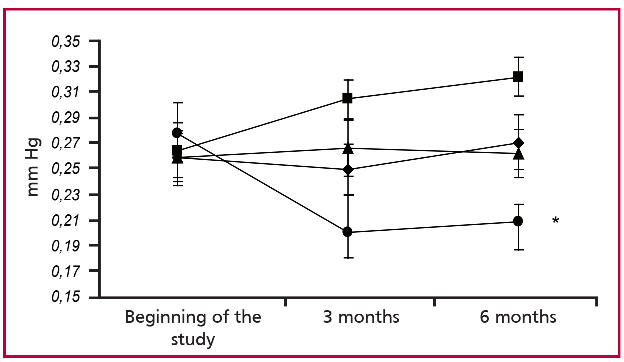

Fig. 4. Outcomes of the aortic valve area by group during follow-up. (■) CG, (●) HT group, (•) HT+R group and (▲) HT+R+C group. * $p < 0.001$ vs. CG.

Table 1. Preoperative variables

		Control	HTG	HT+R	HT+R+C
AVA (cm2)	Baseline	0,264 ± 0,022	0,277 ± 0,024	0,259 ± 0,019	0,259 ± 0,021
	3 months	0,305 ± 0,015	0,2 ± 0,029*†	0,266 ± 0,022	0,249 ± 0,02
	6 months	0,322 ± 0,016	0,208 ± 0,014*†	0,262 ± 0,019	0,271 ± 0,021
LT (mm)	Baseline	0,48 ± 0,02	0,5 ± 0,02	0,5 ± 0,01	0,47 ± 0,01
	3 months	0,5 ± 0,02	0,58 ± 0,02*†	0,53 ± 0,02	0,52 ± 0,02
	6 months	0,49 ± 0,02	0,62 ± 0,02‡†	0,48 ± 0,01	0,54 ± 0,02
Peak gradient (mm Hg)	Baseline	10,6 ± 1,1	9,8 ± 1,3	10,1 ± 1,3	9,3 ± 1,2
	3 months	9,6 ± 1,2	20,5 ± 3,6*†	13,5 ± 2,4	12,1 ± 2,9
	6 months	9,3 ± 1	21,2 ± 3,4*†	10,1 ± 1	13,7 ± 3,9
Mean gradient (mm Hg)	Baseline	5,8 ± 0,7	5,5 ± 1	5,8 ± 0,7	4,8 ± 1,2
	3 months	5,1 ± 0,6	10,6 ± 1,7*†	7,3 ± 1,3	6,4 ± 1,7
	6 months	5,1 ± 0,6	11 ± 1,7*†	5,4 ± 0,7	7 ± 1,8
LVDD (cm)	Baseline	1,27 ± 0,04	1,29 ± 0,05	1,28 ± 0,04	1,32 ± 0,04
	3 months	1,31 ± 0,05	1,24 ± 0,05	1,4 ± 0,07	1,3 ± 0,04
	6 months	1,34 ± 0,4	1,3 ± 0,07	1,31 ± 0,04	1,32 ± 0,04
LVSD (cm)	Baseline	0,85 ± 0,04	0,82 ± 0,03	0,86 ± 0,03	0,77 ± 0,04
	3 months	0,9 ± 0,04	0,77 ± 0,05	0,9 ± 0,07	0,85 ± 0,06
	6 months	0,9 ± 0,04	0,78 ± 0,04	0,87 ± 0,04	0,92 ± 0,04
IVS (cm)	Baseline	0,28 ± 0,01	0,29 ± 0,01	0,29 ± 0,01	0,29 ± 0,01
	3 months	0,29 ± 0,01	0,33 ± 0,01*†	0,33 ± 0,02*	0,31 ± 0,02
	6 months	0,3 ± 0,01	0,34 ± 0,01*†	0,31 ± 0,01	0,31 ± 0,01
PW (cm)	Baseline	0,27 ± 0,01	0,29 ± 0,01	0,3 ± 0,01	0,28 ± 0,01
	3 months	0,28 ± 0,01	0,32 ± 0,02	0,32 ± 0,02	0,32 ± 0,02
	6 months	0,3 ± 0,01	0,34 ± 0,02	0,32 ± 0,01	0,33 ± 0,02
LVM (g)	Baseline	4,5 ± 0,2	4,4 ± 0,4	4,7 ± 0,4	4,7 ± 0,3
	3 months	4,6 ± 0,3	5,6 ± 0,6	5,7 ± 0,5	5,3 ± 0,3
	6 months	4,9 ± 0,3	6,2 ± 0,7	5,4 ± 0,3	5,4 ± 0,4
LVMI (g/kg)	Baseline	1,31 ± 0,05	1,31 ± 0,06	1,32 ± 0,05	1,31 ± 0,06
	3 months	1,33 ± 0,05	1,59 ± 0,11	1,41 ± 0,04	1,43 ± 0,05
	6 months	1,43 ± 0,03	1,78 ± 0,13*†	1,42 ± 0,06	1,36 ± 0,09

AVA: Aortic valve area. LVDD: Left ventricular diastolic dimension. LVSD: Left ventricular systolic dimension. LT: Leaflet thickness. IVS: Interventricular septum thickness. LW: Left wall thickness. LVM: Left ventricular mass. LVMI: Left ventricular mass index. One-way repeated measures analysis of variance (OWRMANOVA). * $p < 0.05$ vs. baseline in the same group; † $p < 0.05$ vs. control during the same time interval; ‡ $p < 0.005$ vs. baseline in the same group.

agent was specifically developed: these actions are called pleiotropic effects. (17, 29-31) Of importance, the groups treated with rosuvastatin had a significant reduction in blood pressure levels (16 mm Hg in SBP and 8 mm Hg in DBP) compared to HTG. Statins might exert some influence on blood pressure in vivo by several mechanisms: improving endothelial dysfunction, (32-36), reducing the inflammatory profile (29-31, 37) and modulating the renin-angiotensin-aldosterone system. (34, 38) Independently of the mechanism of action involved, the antihypertensive effect of rosuvastatin is not affected by cholesterol titration and may have probably contributed to the benefit observed on the aortic valve. Yet, the drug may have a direct action on valvular gene expression regulation that cannot be ruled out. In fact, Kang et al. reported that rosuvastatin reduces angiotensin II-mediated cardiomyocyte hypertrophy via inhibition of LOX-1 (lectin-like oxidized LDL receptor), (39) a specific receptor for oxLDL, constituting an attractive molecular mechanism to explore in AS caused by hypertension.

CONCLUSIONS

The results of this study provide evidence about a potential benefit of statins in the protection of aortic valve damage caused by HT, particularly through pleiotropic effects. Future studies should evaluate the role of these effects on the clinical impact of statins in cardiovascular prevention.

RESUMEN

La rosuvastatina atenúa la progresión de la estenosis aórtica generada por hipertensión arterial, independientemente de sus efectos hipolipemiantes

Introducción

Existe evidencia epidemiológica que vincula factores de riesgo cardiovascular con la estenosis valvular aórtica. Recientemente se ha demostrado el desarrollo de estenosis valvular aortic en un modelo de hipertensión arterial en animales. Planteamos la hipótesis de que el tratamiento con rosuvastatina modifica esta transformación.

Objetivo

Evaluar el efecto de la rosuvastatina sobre el desarrollo de estenosis valvular aórtica.

Material y métodos

Se instrumentaron conejos NZ machos (n = 43) con el modelo 1-riñón 1-clip de Goldblatt para generar hipertensión arterial. Los animales fueron aleatorizados a: HT (n = 17) que no recibió otro tratamiento, HT+R (n = 14) tratado con rosuvastatina 2,5 mg/kg/día y HT+R+C (n = 12) tratado con rosuvastatina 2,5 mg/kg/día + suplemento de colesterol dietético para mantener los niveles basales de colesterol plasmático. Un grupo control (GC) fue sometido a cirugía simulada (n = 15). Las características de la válvula aórtica se midieron por ecografía en condiciones basales y a los 3 y a los 6 meses de hipertensión arterial.

Resultados

A los 6 meses de seguimiento, los incrementos de PAS y PAD fueron más elevados en HT (49% y 40%, respectivamente; p < 0,001) en comparación con los grupos tratados con rosuvastatina (PAS = 23% y 25%; PAD = 28% y 26%; p < 0,001 para HT+R y HT+R+C, respectivamente). El colesterol total se redujo el 45,7% (p < 0,01) sólo en HT+R. El espesor valvar se incrementó en HT (0,50 ± 0,01 vs. 0,62 ± 0,02 mm; p < 0,01), sin mostrar diferencias en HT+R y HT+R+C. Finalmente, el área valvular aórtica mostró una reducción en HT (0,277 ± 0,024 vs. 0,208 ± 0,014 cm2; p < 0,05), sin cambios en HT+R y HT+R+C y un aumento no significativo en el GC (0,264 ± 0,022 vs. 0,32 ± 0,016 cm2; p = 0,07).

Conclusión

La rosuvastatina atenúa la progresión de la estenosis valvular aórtica generada por hypertension arterial. Esta protección podría ser mediada por efectos no hipolipemiantes de estas drogas.

Palabras clave > Estatinas - Estenosis de la válvula aórtica Hipertensión - Dislipidemias - Efectos pleiotrópicos.

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