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Hypertension and Statins

Beneficial Pleiotropic Vascular Effects of Rosuvastatin in Two Hypertensive Models

Dinko Susic, MD, PHD, Jasmina Varagic, MD, PHD, Jwari Ahn, MD, Michael Slama, MD, Edward D. Frohlich, MD

New Orleans, Louisiana

OBJECTIVES The goal of this research was to study the effects of rosuvastatin on systemic and regional hemodynamics in two hypertensive rat models, one genetic, the other induced with inhibition of nitric oxide synthesis.

BACKGROUND Rats naturally have low cholesterol levels that are generally unaffected by statin therapy, thus providing a good model for studying cardiovascular effects unrelated to lipid metabolism.

METHODS Male 20-week-old spontaneously hypertensive rats (SHR) were divided into five groups and given either vehicle or 1, 5, 10, and 20 mg/kg of rosuvastatin daily, by gavage, for 12 weeks. Wistar-Kyoto rats (WKY) were divided into four groups; the first received vehicle and the second rosuvastatin (20 mg/kg). The third and fourth groups were given N^{ω}-nitro-L-arginine (L-NAME) (15mg/kg/day) in drinking water, and the fourth group received rosuvastatin daily, 20 mg/kg for six weeks. At the end of the respective treatments, systemic and organ hemodynamics (radionuclide-labeled microspheres) and cardiovascular mass were determined in all rats.

RESULTS Rosuvastatin reduced arterial pressure in SHR rats, but not in WKY/L-NAME rats. Total peripheral resistance decreased with rosuvastatin in both hypertensive models, whereas cardiac output increased with rosuvastatin in WKY/L-NAME rats. Neither cardiac nor aortic mass was changed. Regional hemodynamics improved with rosuvastatin in both hypertensive models, as evidenced by increased blood flows and decreased vascular resistances. No effect on plasma lipids was observed.

CONCLUSIONS These results showed that rosuvastatin reduced arterial pressure in genetic hypertension and improved systemic and regional hemodynamics in both hypertensive models independently of cholesterol levels. Thus rosuvastatin improved systemic and regional hemodynamics by reducing vascular resistance. (J Am Coll Cardiol 2003;42:1091–7) © 2003 by the American College of Cardiology Foundation

There is accumulating evidence that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, exert numerous beneficial effects that are apparently independent of their action on blood lipids (1–3). These include effects on the cardiovascular system, kidneys, bone, and glucose metabolism. A number of clinical trials have shown that statins significantly reduce cardiovascular morbidity and mortality. Potential mechanisms that may mediate beneficial cardiovascular action of statins include modulation of endothelial function (4–7), anti-inflammatory action (8,9), antioxidant properties (10), plaque stabilization (11), and effects on thrombosis (12) and vasculogenesis (13). It is also worth noting that, although statins share a common lipid-lowering effect, there seem to be differences within this class of drugs, not only in their lipid-lowering potential, but also in their nonlipid effects (14). These potential differences necessitate careful and systematic studies involving each member of the statin family.

In the present study we examined cardiovascular effects of rosuvastatin, a new HMG-CoA reductase inhibitor (15). To this end, the effects of rosuvastatin on systemic and regional hemodynamics were studied in spontaneously hypertensive (SHR) rats, normotensive (Wistar-Kyoto; WKY) rats, and in WKY in which endothelial function had been compromised by the administration of N^{ω}-nitro-L-arginine (L-NAME) (16), an inhibitor of nitric oxide synthesis. Because plasma lipid levels are normally low in rats (in contrast with human beings) and because statins usually do not modify lipid profile in rats, they provide an excellent model for studying the other cardiovascular effects of statins.

METHODS

Animals. Adult male WKY and SHR rats were obtained from Charles River Breeding Laboratories (Wilmington, Massachusetts). They were housed in a temperature and humidity controlled facility with 12 h light/dark cycle. Standard rat chow (PMI Nutrition International, St. Louis, Missouri) and tap water were provided ad libitum unless stated otherwise. Our Institutional Animal Care and Use Committee had approved the study in advance.

Experimental protocol. Two experiments were performed: one in the SHR with naturally occurring hypertension and

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Abbreviations and Acronyms
L-NAME = N^{ω}-nitro-L-arginine
SHR = spontaneously hypertensive rats
WKY = Wistar-Kyoto rats

the other in the normotensive WKY and WKY in which hypertension was induced with L-NAME (Sigma Chemical Co., St. Louis, Missouri), an inhibitor of nitric oxide synthesis.

In the first experiment, the effects of four different doses of rosuvastatin (Crestor) (AstraZeneca, Macclesfield, Cheshire, England) on systemic and organ hemodynamics and cardiovascular mass in SHR were studied. To this end, male, 23-week-old SHR were randomly divided into five groups, 15 rats in each. The control group did not receive any treatment; rats in the other four groups were given rosuvastatin daily by gavage, at 1, 5, 10, and 20 mg/kg dose levels, respectively. Rosuvastatin was dissolved in distilled water immediately before use and was administered within the next one-half hour. Rats were treated for 12 weeks, and, at the end, studies on systemic and regional hemodynamics were performed as described in the following text.

The second experiment was performed in adult, 23-week-old male WKY rats that were divided into four groups, with 10 rats in each. The control group received no treatment, whereas the second group was given rosuvastatin, 20 mg/kg/day by gavage. The third and fourth groups were given L-NAME in drinking water, but, in addition, the fourth group received rosuvastatin daily, 20 mg/kg. Initial concentration of L-NAME in drinking water was 200 mg/l. The concentration for each rat was then adjusted every second day (based on fluid intake) so that the rats ingested approximately 15 mg/kg/day of L-NAME throughout the study. Treatment lasted for six weeks, and hemodynamic studies were performed at the end.

Hemodynamic studies. At the end of treatment, the rats were anesthetized with pentobarbital (40 mg/kg) and then instrumented for the determination of systemic and regional hemodynamics (using the reference standard radiomicrosphere method) as detailed elsewhere (17–19). In brief, a jugular vein, femoral artery, and the left ventricle (via right carotid artery) were cannulated with polyethylene catheters (PE-50) filled with a heparinized 1% NaCl solution and were exteriorized at the nape of the neck through a subcutaneous tunnel. Rats were then placed into nonrestrictive polyethylene cages where they were allowed to recover for 3 to 5 h (17–19).

The baseline measurements of systemic and coronary hemodynamics were obtained while unrestrained, after full recovery from anesthesia. Thus, the femoral arterial catheter was connected to a pressure transducer (P23Db; Statham Instruments, Oxnard, California), and arterial pressure was recorded on a multichannel physiograph (Sensor Medics R612, Yorba Linda, California) while, simultaneously, heart rate was derived through a tachometer coupler. Cardiac output was measured using the reference sample microsphere method as reported previously (17–19). Cardiac index was calculated from cardiac output and body weight and expressed in ml/min/kg. Total peripheral resistance index (U/kg) was calculated by dividing mean arterial pressure by cardiac index. Blood flow to different organs including heart, lungs, liver, kidneys, skeletal muscle, skin, and brain was determined on the basis of percentage distribution of the radiolabeled (113Sn) microspheres to each organ at the end of the study (17–19). The method has been validated previously (17).

After the baseline measurements were obtained, maximal coronary vasodilation was produced by dipyridamole infusion (4 mg/kg/min, intravenous for 10 min) (18,19) using a Harvard infusion/withdrawal pump (Harvard Apparatus, South Natick, Massachusetts). The hemodynamic studies were repeated using microspheres having a second radionuclide (46Sc). At the conclusion of the study, rats were killed with an overdose of pentobarbital, and, immediately thereafter, the heart, aorta, lungs, liver, kidneys, brain, and samples of skin and skeletal muscle were removed and weighed. Blood samples were taken for lipid profile measurements. Tissue samples, as well as blood reference samples, were placed in plastic scintillation vials and were counted for 15 min in a deep-well gamma scintillation spectrometer (Packard, Downer Grove, Illinois) having a multichannel analyzer. Spillover correction between channels was achieved using matrix inversion software (Compusphere, Packard, Downer Grove, Illinois). Organ blood flows were calculated by multiplying the fractional distribution of radioactivity to each organ by cardiac output. They were normalized for the wet weight of the respective organ

Table 1. BW, LWI, RVI, and AWI of Spontaneously Hypertensive Rats, Either Control or Treated With 1, 5, 10, and 20 mg/kg/day of R

Indexes	Control (n = 12)	R 1 mg/kg (n = 14)	R 5 mg/kg (n = 13)	R 10 mg/kg (n = 13)	R 20 mg/kg (n = 13)
BW (g)	353 ± 9	361 ± 9	354 ± 5	355 ± 8	352 ± 7
LWI (mg/g)	3.01 ± 0.04	3.02 ± 0.07	3.02 ± 0.06	3.05 ± 0.02	3.06 ± 0.03
RWI (mg/g)	0.55 ± 0.03	0.55 ± 0.02	0.54 ± 0.02	0.52 ± 0.01	0.50 ± 0.03
AWI (mg/mm)	1.23 ± 0.03	1.22 ± 0.03	1.23 ± 0.02	1.17 ± 0.03	1.21 ± 0.02

Values are means ± 1 SEM.
AWI = aortic weight index; BW = body weight; LWI = left ventricular weight index; R = rosuvastatin; RVI = right ventricular weight index.

Table 2. SAP, DAP, MAP, HR, CI, and TPR in Spontaneously Hypertensive Rats, Either Control or Treated With 1, 5, 10, and 20 mg/kg/day of R

Indexes	Control (n = 12)	R 1 mg/kg (n = 14)	R 5 mg/kg (n = 13)	R 10 mg/kg (n = 13)	R 20 mg/kg (n = 13)
SAP (mm Hg)	240 ± 5	227 ± 4	219 ± 4*	215 ± 5*	216 ± 4*
DAP (mm Hg)	162 ± 4	153 ± 4	147 ± 3*	133 ± 6*	138 ± 5*
MAP (mm Hg)	188 ± 5	175 ± 4	165 ± 5*	157 ± 5*	163 ± 4*
HR (beats/min)	405 ± 6	408 ± 5	396 ± 6	388 ± 5	392 ± 5
CI (ml/min/kg)	272 ± 7	271 ± 10	266 ± 5	255 ± 5	259 ± 8
TPR (U/kg)	0.70 ± 0.02	0.66 ± 0.04	0.62 ± 0.02*	0.59 ± 0.03*	0.61 ± 0.02*

Values are means ± 1 SEM. *$p < 0.05$ when compared with control group.
CI = cardiac index; DAP = diastolic arterial pressure; HR = heart rate; MAP = mean arterial pressure; R = rosuvastatin; SAP = systolic arterial pressure; TPR = total peripheral resistance.

and expressed as ml/min/g. Regional vascular resistances were calculated by dividing the mean arterial pressure by the respective organ blood flows and then normalized for that organ weight (expressed as U/g). Blood flow reserve for the right and left ventricles was calculated as the difference between the baseline and dipyridamole infusion flows. Minimal vascular resistance was defined as vascular resistance achieved by dipyridamole.

Myocardial collagen content. As an estimate of collagen content, hydroxyproline concentration was determined in left ventricular samples, as described previously (18). Hydroxyproline concentration was expressed as mg/g dry weight.

Statistical analysis. Values are expressed as the mean ± 1 SEM. The one-way analysis of variance and Bonferroni's modification of *t* test were used to test the significance of differences between the groups (20). The 5% (or less) confidence level was considered to be of statistical significance.

RESULTS

Body, cardiac, and aortic masses in SHR. No differences in body weight, left and right ventricular mass indexes, and aortic mass index were found between groups (Table 1).

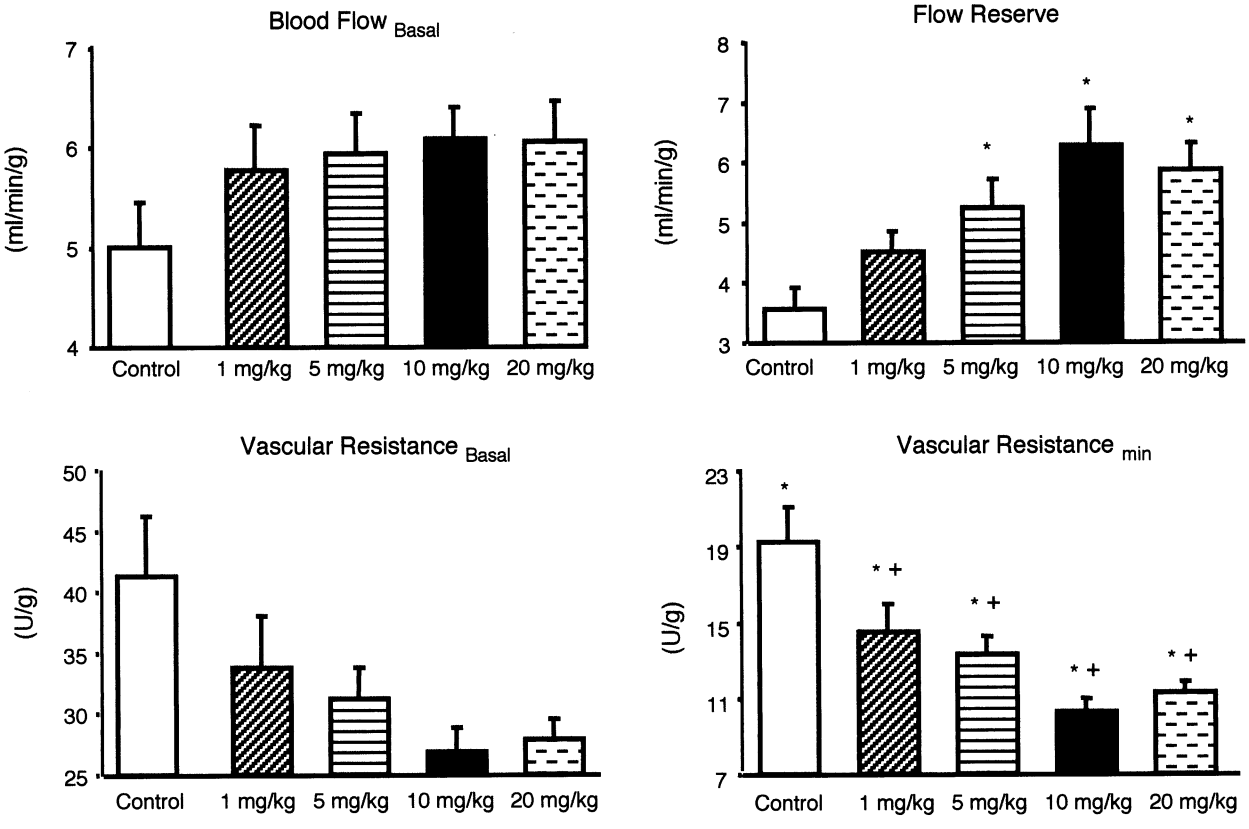

Figure 1. Left ventricular coronary hemodynamics in control spontaneously hypertensive rats and rats treated with 1, 5, 10, or 20 mg/kg/day of rosuvastatin for 12 weeks. Twelve to 14 rats per group. Values are means ± 1 SEM. *$p < 0.05$ when compared with the value under basal conditions; +$p < 0.05$ when compared with control group.

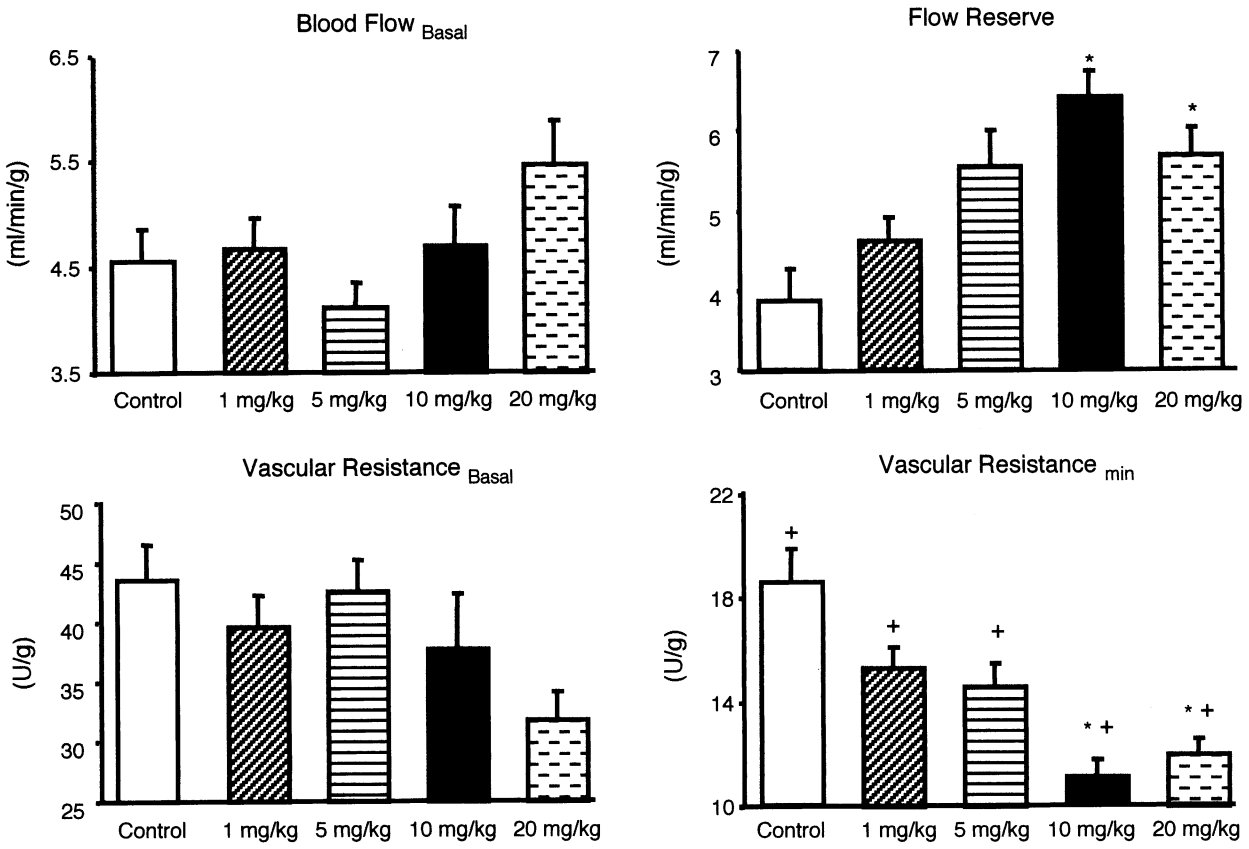

Figure 2. Right ventricular coronary hemodynamics in control spontaneously hypertensive rats and rats treated with 1, 5, 10, or 20 mg/kg/day of rosuvastatin for 12 weeks. Twelve to 14 rats per group. Values are means ± 1 SEM. *$p < 0.05$ when compared with the value under basal conditions; +$p < 0.05$ when compared with control group.

Hydroxyproline concentration was determined in eight untreated SHR and eight SHR given 10 mg/kg of rosuvastatin and, similarly, no difference was found (3.22 ± 0.21 mg/g in control vs. 3.11 ± 0.18 in rosuvastatin-treated rats).

Systemic hemodynamics in SHR. Rosuvastatin decreased systolic, diastolic, and mean arterial pressures in a dose-dependent manner up to the 10 mg/kg dose (Table 2). The higher dose had no additional effects. Cardiac output and heart rate were unaffected, but total peripheral resistance was lower in rats treated with rosuvastatin (Table 2).

Coronary hemodynamics in SHR. Left ventricular coronary hemodynamic indexes are presented in Figure 1. Although rosuvastatin had no significant effect on baseline blood flows or vascular resistances, it significantly increased coronary flow reserve and decreased minimal coronary vascular resistance. This effect appeared to be dose-dependent, with a maximal effect being achieved at the 10 mg/kg level. Right ventricular coronary hemodynamics paralleled those changes in the left ventricle (Fig. 2).

Other regional hemodynamics in SHR. The effects of prolonged administration of rosuvastatin on blood flows and vascular resistances in the kidney, liver, skin, skeletal muscle, and brain are presented in Table 3. Rosuvastatin did not affect basal flow or resistance in any of those organs. However, it did decrease minimal vascular resistance in the kidneys, muscle, and brain, but not in the liver and skin.

Lipid profile in SHR. Rosuvastatin treatment did not affect plasma levels of total cholesterol, high-density lipoprotein, low-density lipoprotein, or triglycerides (Table 4).

Systemic and regional hemodynamics in WKY and WKY given L-NAME. There were no hemodynamic changes produced by rosuvastatin on systemic or coronary hemodynamics in the normotensive WKY rats (Table 5). Six weeks of treatment with L-NAME produced an increase in arterial pressure and total peripheral resistance and a decrease in cardiac output in WKY. Simultaneously, a deterioration of hemodynamic variables, as indicated by a decrease in blood flows and increased vascular resistances, occurred in all examined organs, including kidney, skin, skeletal muscle, and heart. Of particular interest in these L-NAME–treated rats was the finding that, although rosuvastatin did not lower arterial pressure, it significantly improved cardiac output, total peripheral resistance, and regional hemodynamics. Left ventricular mass did not increase in WKY rats treated with L-NAME (2.57 ± 0.03 mg/g vs. 2.52 ± 0.04 mg/g, in controls and L-NAME WKY rats, respectively) nor did rosuvastatin affect left ventricular mass in the L-NAME–treated rats (2.52 ± 0.04 vs. 2.46 ± 0.05, respectively).

Table 3. BF and VR under Basal Conditions and MVR (After Dipyridamole Infusion) in Kidney, Liver, Skin, Muscle, and Brain of SHR Rats, Either Control or Treated With 1, 5, 10, and 20 mg/kg/day of R

	Control (n = 12)	R 1 mg/kg (n = 14)	R 5 mg/kg (n = 13)	R 10 mg/kg (n = 13)	R 20 mg/kg (n = 13)
Kidney					
BF (ml/min/g)	7.02 ± 0.29	6.82 ± 0.33	7.08 ± 0.33	7.21 ± 0.54	6.85 ± 0.34
VR (U/g)	27.7 ± 1.1	26.6 ± 1.7	23.9 ± 1.4	23.3 ± 1.8	24.3 ± 1.0
MVR (U/g)	23.7 ± 1.2	17.4 ± 0.7*†	16.8 ± 1.0*†	15.3 ± 0.8*†	16.6 ± 0.8*†
Liver					
BF (ml/min/g)	0.22 ± 0.02	0.20 ± 0.2	0.21 ± 0.3	0.28 ± 0.3	0.23 ± 0.03
VR (U/g)	926 ± 65	940 ± 94	920 ± 116	794 ± 124	824 ± 90
MVR (U/g)	781 ± 147	746 ± 99	620 ± 66	622 ± 169	703 ± 125
Skin					
BF (ml/min/g)	0.09 ± 0.01	0.10 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.08 ± 0.01
VR (U/g)	2,135 ± 130	1,853 ± 135	2,100 ± 145	1,920 ± 136	2,095 ± 113
MVR (U/g)	2,306 ± 165	1,892 ± 114	2,332 ± 210	2,075 ± 142	2,112 ± 153
Skeletal muscle					
BF (ml/min/g)	0.10 ± 0.01	0.11 ± 0.02	0.10 ± 0.01	0.10 ± 0.01	0.10 ± 0.01
VR (U/g)	2,111 ± 187	2,056 ± 244	1,861 ± 131	1,725 ± 101	1,827 ± 136
MVR (U/g)	1,682 ± 134	1,161 ± 105*†	1,225 ± 136*†	855 ± 67*†	920 ± 102*†
Brain					
BF (ml/min/g)	0.97 ± 0.03	0.99 ± 0.07	1.00 ± 0.08	1.11 ± 0.08	1.00 ± 0.07
VR (U/g)	197 ± 7	190 ± 16	176 ± 14	153 ± 13*	172 ± 12
MVR (U/g)	183 ± 8	155 ± 12	144 ± 11*	118 ± 10*	133 ± 8*

Values are means ± 1 SEM. *$p < 0.05$ when compared with control group. †$p < 0.05$ when compared with the value under basal conditions.

BF = blood flow; MVR = minimal vascular resistance; R = rosuvastatin; SHR = spontaneously hypertensive rats; VR = vascular resistance.

DISCUSSION

The results of this study clearly demonstrate that rosuvatatin exerts beneficial cardiovascular effects in SHR, including lowering of arterial pressure and peripheral resistance in a dose-dependent manner. These hemodynamic changes were independent of its lipid action. The pressure-lowering effects of various statins have been reported previously in angiotensin II-induced hypertension in rats (21), SHR rats (22), as well as in hypertensive patients (23). In the present study, the pressure-reducing effect of rosuvastatin in SHR was mediated via a decrease in peripheral resistance, cardiac output remaining unaffected. Interestingly, in the WKY rats rendered hypertensive by L-NAME, rosuvastatin failed to reduce arterial pressure but significantly reduced vascular resistance. Simultaneously, rosuvastatin significantly improved the L-NAME–induced decrease in cardiac output and thereby kept pressure unchanged. Furthermore, it appears that the beneficial effect of rosuvastatin on cardiac output in the WKY/L-NAME rats was, at least in part, mediated by improved coronary blood flow. Thus, coronary blood flow was markedly decreased in rats treated with L-NAME, which may have produced ventricular ischemia with depression of systolic function and decreased cardiac output. Rosuvastatin improved coronary flow, which may have improved ventricular function and cardiac output in these WKY/L-NAME rats. In addition, the rosuvastatin-induced decrease in vascular resistance may have contributed to improvements in cardiac output by increasing venous return.

Table 4. Plasma Levels of Chol, HDL, LDL, or Trigl in Control SHR and SHR Treated With 10 or 20 mg/kg/day of R

	Control (n = 8)	R 10 mg/kg (n = 8)	R 20 mg/kg (n = 8)
Chol (mg/dl)	34 ± 2	32 ± 1	30 ± 2
HDL (mg/dl)	15 ± 1	18 ± 1	16 ± 1
LDL (mg/dl)	16 ± 1	17 ± 1	17 ± 1
Trigl (mg/dl)	18 ± 1	22 ± 2	19 ± 1

Values are means ± 1 SEM.

Chol = cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; R = rosuvastatin; SHR = spontaneously hypertensive rats; Trigl = triglycerides.

Rosuvastatin reduced total peripheral vascular resistance in both hypertensive models. Our results do not point to the mechanism of this vasodilatory effect of rosuvastatin, but it certainly is conceivable that an improvement in endothelial function may mediate this action, particularly in the already endothelial-compromised WKY/L-NAME rats (4–7,24). Other mechanisms are also possible. Thus, some statins have been shown to downregulate angiotensin II type 1 receptors in vascular smooth muscle (25), ameliorate angiotensin II-induced vascular injury (26), and increase nitric oxide production in coronary vasculature (27). It is also worth noting that rosuvastatin reduced minimal vascular resistance (measured after infusion of a vasodilator) in all organs examined with the exception of liver and skin. This finding may indicate that regional differences in the vascular effects of rosuvastatin may exist.

We have shown previously that coronary hemodynamics are impaired in 35-week-old SHR; basal blood flow was unaffected, but minimal coronary vascular resistance was

Table 5. MAP, CI, TPRI, RBF, RVR, SBF and SVR, MBF and MVR, CBF and CVR, MCVR, and CFR in Control WKY, WKY Given Rosuvastatin for Six Weeks, WKY Treated With L-NAME for Six Weeks, and WKY Given L-NAME and Rosuvastatin for Six Weeks

	WKY (n = 10)	WKY + R (n = 8)	L-NAME (n = 8)	L-NAME + R (n = 9)
MAP (mm Hg)	99 ± 6	106 ± 7	156 ± 5*	152 ± 8*†
CI (ml/min/kg)	268 ± 38	273 ± 27	119 ± 15*	172 ± 10*†
TPRI (U/kg)	0.37 ± 0.06	0.39 ± 0.05	1.42 ± 0.26*	0.91 ± 0.06*†
RBF (ml/min/g)	7.99 ± 0.32	8.33 ± 0.29	2.57 ± 0.37*	4.19 ± 0.21*†
RVR (U/g)	12.5 ± 0.7	12.9 ± 0.6	60.8 ± 1.5*	36.8 ± 3.5*†
SBF (ml/min/g)	0.12 ± 0.01	0.13 ± 0.01	0.03 ± 0.00*	0.04 ± 0.00*
SVR (U/g)	820 ± 43	812 ± 27	5,180 ± 297*	4,542 ± 354*
MBF (ml/min/g)	0.13 ± 0.01	0.14 ± 0.01	0.04 ± 0.00*	0.07 ± 0.00*†
MVR (U/g)	733 ± 54	737 ± 43	3,873 ± 288*	2,356 ± 201*†
CBF (ml/min/g)	5.95 ± 0.14	5.73 ± 0.12	3.49 ± 0.18*	4.37 ± 0.38*†
CVR (U/g)	17.3 ± 0.4	18.4 ± 0.3	45.1 ± 2.9*	34.9 ± 3.28*†
MCVR (U/g)	7.41 ± 0.29	7.96 ± 0.4	34.9 ± 2.4*	18.3 ± 1.8*†
CFR (ml/min/g)	6.38 ± 0.12	7.21 ± 0.13	1.09 ± 0.24*	3.89 ± 0.48*†

Values are means ± 1 SEM. *$p < 0.05$ when compared with control group. †$p < 0.05$ when compared with the value under basal conditions.

CBF = coronary blood flow; CFR = coronary flow reserve; CI = cardiac index; CVR = coronary blood resistance; MAP = mean arterial pressure; MBF = skeletal muscle blood flow; MCVR = minimal coronary vascular resistance; MVR = muscle vascular resistance; R = rosuvastatin; RBF = renal blood flow; RVR = renal vascular resistance; SBF = skin blood flow; SVR = skin vascular resistance; TPRI = total peripheral resistance index; WKY = Wistar-Kyoto rats.

increased, and coronary flow reserve was decreased as compared with normotensive WKY controls of the same age (28). Our present findings confirm this observation. Furthermore, the results show that rosuvastatin significantly improved coronary hemodynamics by decreasing minimal vascular resistance and increasing flow reserve in both hypertensive models. It is conceivable that the improvement in endothelial function (4–7,24), together with antioxidant (10), and anti-inflammatory actions exerted by some statins, may have contributed to that effect.

There was no effect of rosuvastatin on cardiovascular mass in SHR. Thus, there was no difference in right or left ventricular weight index, or aortic weight index between the control and rosuvastatin-treated groups. Similarly, no effect of rosuvastatin on ventricular collagen concentration was observed in SHR. Furthermore, rosuvastatin did not affect left ventricular mass in L-NAME–treated rats. These findings are inconsistent with other studies in which statins have been shown to reduce cardiac mass and ventricular collagen concentration in rats with aortic stenosis (29), prevent angiotensin II-induced cardiac myocyte hypertrophy in tissue culture (30), and reduce collagen type 1 expression in the hearts of rats with myocardial infarction (31). It is possible that differences in properties of statins employed in these studies account for the divergent results. Possibly a more likely explanation would be that differences in experimental models may be responsible for these divergent findings. Thus, the antihypertrophic and antifibrotic effects of some statins have been shown in angiotensin II-dependent models (28–30), whereas the present study involves models with naturally occurring or experimentally induced endothelial dysfunction.

Study limitations. Our study is not devoid of potential limitations. The doses of rosuvastatin used in the present study were very high when compared with doses used in human medicine. The most effective doses in our study (10 and 20 mg/kg/day) were 10 to 20 × higher than the maximal recommended dose in patients. Thus, one might question the physiologic relevance of our findings. However, it should be pointed out that, in general, doses of various drugs used in rat studies are 50 to 100 times higher that those used in human medicine. For instance, the effective dose of hydrochlorothiazide in rats is 80 mg/kg versus about 1 mg/kg in patients; metoprolol dose in rats is 150 mg/kg versus 1 to 2 mg/kg in patients; lisinopril dose in rats is 20 mg/kg versus 0.1 to 0.5 mg/kg in patients. Thus, by inference, the fact that the dose of rosuvastatin was high does not by itself abolish relevance of our data. It is also worth noting that, although rosuvastatin did not affect plasma cholesterol levels in our study, we cannot exclude the possibility that the effects of rosuvastatin were mediated via its effect on lipid metabolism.

Conclusions. In conclusion, our data demonstrated that rosuvastatin reduced arterial pressure in genetic hypertension and improved systemic and regional hemodynamics in the genetic model as well as in L-NAME–induced hypertension independent of its lipid action. It seems likely that this beneficial effect was mediated by amelioration of endothelial dysfunction present in both experimental hypertensive models, although other mechanisms are possible.

Reprint requests and correspondence: Dr. Dinko Susic, Division of Research, Ochsner Clinic Foundation, 1520 Jefferson Highway, New Orleans, Louisiana 70121. E-mail: dsusic@ochsner.org.

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