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Life Survival and Cardiovascular Structures Following Selective β-Blockade in Spontaneously Hypertensive Rats

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The aim of this study was to assess life survival, and arterial and cardiac structural changes following chronic selective β-blockade in spontaneously hypertensive rats (SHR). Twenty-two SHR aged 3 months and 20 SHR aged 18 months were treated with the β_1-blocking agent bisoprolol (10 mg/kg/day) or placebo for a period of 2 months. At the end of this period left and right ventricular weight and morphometric parameters of five different arterial segments (thoracic and abdominal aorta, renal, mesenteric, and carotid arteries) were evaluated. In younger SHR, systolic blood pressure (tail-cuff method) was significantly lower in drug-treated animals (225 ± 15 *v* 185 ± 10 mm Hg in placebo-treated animals; $P < .001$); left ventricular weight was significantly lower in drug-treated rats (0.845 ± 0.02 *v* 0.932 ± 0.03 g; $P < .05$); medial thickness was significantly lower in the bisoprolol-treated rats at the site of the thoracic (−22%) and abdominal (−17%) aorta, and mesenteric artery (−29%); in the renal and carotid arteries, no change in medial thickness was observed. In older SHR, cardiovascular morbidity and mortality were significantly higher ($P < .01$) in the placebo group. In bisoprolol-treated animals, systolic blood pressure did not change and was even significantly higher than in controls. Heart weight and medial thickness of the thoracic aorta and the renal arteries were significantly lower in the Bisoprolol group. These results provide evidence that 2 months of selective β-blockade in adult SHR has an important antihypertrophic cardiac and vascular effect. The differences observed among the studied arterial segments cannot be due to blood pressure changes and may be related to intrinsic structural particularities or different influences of the adrenergic tone. In older animals, the structural changes were associated with a significant improvement of life survival, together with decrease in the development of heart failure. Am J Hypertens 1994;7: 186–192.

KEY WORDS: **Spontaneously hypertensive rats, selective β-blocking agents, arterial and cardiac structure.**

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The influence of long-term antihypertensive drug treatment on blood pressure and cardiovascular structures has been widely studied in spontaneously hypertensive rats (SHR). There is clear evidence that converting enzyme inhibitors, calcium antagonists, and β-adrenergic blockers suppress the development of cardiac hypertrophy, whereas few changes are obtained using diuretics, hydralazine, or Minoxidil.[1] In the case of

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arterial structure, the situation is less clear. Whereas converting enzyme inhibitors and calcium entry blockers are known to reduce substantially arterial hypertrophy,[2–4] there are no relevant data concerning β-blocking agents. Indeed trophic effects of peripheral adrenergic nerves on vascular structure have been widely described in the literature[5,6] but have been principally related to α- rather than to β-receptors.

In comparison with studies on cardiovascular structure changes, much less is known about the influence of antihypertensive treatment on cardiovascular mortality and life survival in SHR. This lack of knowledge is principally due to the prolonged observation period of about 2 years that is needed to answer this question in SHR. Subsequently, most results stem from studies with calcium antagonists, conventional peripheral vasodilators, converting enzyme inhibitors, and, to a lesser extent, diuretics.[7] Again, little is known about β-adrenergic blockade in this regard.

In the present study, we report our experience on the effect of selective β-blockade on life survival and cardiovascular structure in SHR. The study was performed in two populations of spontaneously hypertensive rats: a younger population of 3 months of age and an older one of 18 months of age. The selective β-blocking agent bisoprolol was used.[8,9] Cardiac and arterial structures, involving such arteries as the aorta, the carotid, the mesenteric, and the renal arteries, were studied using available well-established morphometric techniques.

MATERIALS AND METHODS

Forty-two male SHR (Janvier France Laboratories, France) were divided into two groups: younger (22 SHR of 3 months of age) and older (20 SHR of 18 months of age) animals. In each of these two groups, a randomization was performed: i) in the control group, a standard diet was administered, whereas ii) in the drug group, the bisoprolol was mixed in the standard rat chow at a calculated dose of 20 mg/kg/day. This latter dosage is known to produce an effective decrease in mean blood pressure in SHR treated under standard conditions.[8,9] The arterial pressure was measured every 15 days by a noninvasive method (tail-cuff plethysmography) in all the studied animals. At the end of an 8-week period for the younger SHR and 10 weeks for the older SHR, 10 animals died (see Results below). The remainder were killed and the arterial segments to be studied were fixed under pressure to perform the morphologic study. For that, the following procedure was applied.[10–12] After median thoracotomy and laparotomy, the descending thoracic aorta, the abdominal aorta, the left common carotid artery, the left renal artery, and the inferior mesenteric artery were exposed and carefully dissected. A catheter was introduced into the left carotid artery and connected to a vial containing a solution of glutaraldehyde (2.5%) located above the animal. The vial of glutaraldehyde was placed in such a way to obtain an intraarterial hydrostatic pressure equal to 150 mm Hg. Then, the right auricle was incised and the cannula of infusion was opened. The animal died in the seconds following the beginning of the glutaraldehyde infusion, and within 1–2 min, its circulatory tract was rinsed with the fixation solution. When the liquid coming from the auricle was clear, a clamp on the auricle was positioned, and the vascular system was kept under pressure for 2 hours while adjusting to the eventual leakages. The previously dissected vessels were taken and preserved in a solution of glutaraldehyde.

The vessel samples were included in a gel used for the low-temperature sections (medium of inclusion, Isosystem) and cooled at −20°C. When the gel was solidified, transverse sections of the arterial rings were obtained for each sample. The sections were examined with a microscope. Finally, the sections were photographed at a known amplification (from ×48 for the aorta to ×125 for the small arteries). When the films were developed, the pictures obtained were projected on a digitizer to measure the surface of the vascular lumen as well as the external surface of the vessel. The final amplification used (amplification of the microscope × enlargement of the projector) varied between 160 for the aorta and 520 for the mesenteric artery.

For each sample, the collected results were the surface of the vascular lumen (Si) and the external surface of the vessel defined by the external side of the media (Se). From these values, the cross-sectional area (CSA) of the media was calculated. As a consequence of the incompressibility of the arteries, the value of medial CSA is known to be poorly influenced by fixation pressure.

The rat's heart was also excised to estimate the left and right ventricular weight. The results were normalized by body weight of the animals. The person performing the morphometric study did not know the groups from which the different rats came.

In the present investigation, blood pressure, heart weight, and medial CSA were indeed higher in older than in younger untreated SHR, as previously observed by others.[2,3,5] However, the purpose of this study was exclusively to evaluate cardiovascular structures and life survival in the younger and older group by comparing the bisoprolol- and the placebo-treated animals in each group. The effect of treatment on cardiovascular structures was studied using one-factor ANOVA. In older animals, a χ^2 test was used to evaluate the drug effect on life survival and cardio-

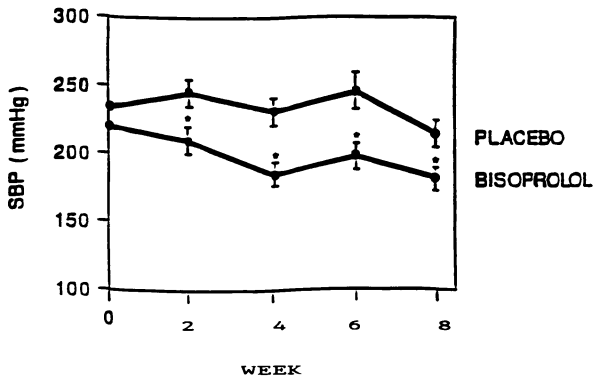

FIGURE 1. *Evolution of systolic blood pressure (SBP) in the younger groups (tail-cuff),* *P < .01.

vascular complications. A P value < .05 was considered significant.

RESULTS

Young Animals Two rats (one per group) presenting abnormal symptoms involving loss of weight and signs of respiratory insufficiency were excluded before the end of the study. Another rat from the placebo group was excluded for technical reasons. Thus, the results are presented as including 9 placebo- and 10 bisoprolol-treated animals. All were living and had no cardiovascular complications.

The systolic blood pressure (SBP) (tail-cuff) changes are summarized in Figure 1. From the second week of treatment, bisoprolol-treated rats presented significantly lower values of SBP than did control rats. This difference persisted until the end of the treatment period (Table 1). The body weights of bisoprolol-treated rats were slightly lower than those of the control rats, but the difference was not significant (Table 1). Left ventricular weight was significantly lower in rats treated with bisoprolol ($P < .05$; Table 1). However, the difference was no longer significant when the ventricle to body weight ratio was calculated (Table 1). Treatment with bisoprolol had no effect on right ventricular weight.

Table 2 summarizes the results observed in the five studied areas. Treatment with bisoprolol was associated with a striking and highly significant antihypertrophic effect on three of the five arterial segments studied: the thoracic aorta, the abdominal aorta, and the mesenteric artery. In these three segments, the cross-sectional areas of the media in the bisoprolol-treated rats were lower by 22%, 17%, and 19%, respectively, as compared with the placebo-treated rats. On the carotid and renal arteries, the differences were less important (respectively, 7.5% and 7%) and not statistically significant.

Older Animals Half of the rats (5 of 10) treated with placebo died before the end of the 2-month treatment period (Figure 2). The deceased rats presented symptoms of congestive heart failure including low blood pressure, loss of weight, and ascites. Among the five remaining placebo-treated animals, four of the five presented low SBP (<150 mm Hg) (Figure 3) after the end of the 20th month. Weight loss was also noted (Table 1). In these five rats, ascites was found when the animals were killed. In the bisoprolol-treated rats, 2 of 10 died, presenting the same symptoms of heart failure as the placebo-treated rats. The remaining eight animals did not show any of these signs. Thus, in the placebo group 9 of 10 rats developed heart failure signs, against 2 of 10 in the bisoprolol group ($P < .01$).

Systolic blood pressure evaluated with the tail-cuff method was much higher in the group of bisoprolol-treated rats ($P < .01$) (Figure 3). Thus, treatment was not able to decrease blood pressure significantly in this type of aged rats.

Bisoprolol-treated animals showed significantly lower values of indexed right ventricular weight ($P < .01$) versus the placebo group. The difference in indexed left ventricular weight was not statistically significant.

TABLE 1. MEAN VALUES OF BODY WEIGHT (BW), LEFT VENTRICULAR WEIGHT (LVW), RIGHT VENTRICULAR WEIGHT (RVW), AND LVW/BW AND RVW/BW RATIOS AFTER 2 MONTHS OF ADEQUATE SELECTIVE β-BLOCKADE

	BW (g)	LVW (g)	LVW/BW (mg/g)	RVW (g)	RVW/BW (mg/g)
Younger animals					
Placebo (n = 9)	399 ± 4	0.932 ± 0.09	2.34 ± 0.23	0.295 ± 0.09	0.75 ± 0.12
Bisoprolol (n = 10)	385 ± 20	0.842 ± 0.08*	2.18 ± 0.18	0.310 ± 0.10	0.80 ± 0.09
Older animals					
Placebo (n = 5)	350 ± 18	1.37 ± 0.14	3.94 ± 0.38	0.875 ± 0.096	2.56 ± 0.26
Bisoprolol (n = 8)	419 ± 20	1.30 ± 0.11	3.14 ± 0.30	0.638 ± 0.075	1.51 ± 0.21**

Values are mean ± 1 standard deviation.

P *values:* * <.05; ** <.01.

TABLE 2. MEDIAL CROSS-SECTIONAL AREA (mm^2) IN YOUNGER AND OLDER ANIMALS AFTER 2 MONTHS OF ADEQUATE SELECTIVE β-BLOCKADE

	Younger	Older
Thoracic aorta		
Placebo	0.505 ± 0.04	1.078 ± 0.02
Bisoprolol	0.392 ± 0.03**	0.947 ± 0.03*
Abdominal aorta		
Placebo	0.247 ± 0.03	0.362 ± 0.016
Bisoprolol	0.205 ± 0.03**	0.340 ± 0.026
Carotid artery		
Placebo	0.105 ± 0.008	0.274 ± 0.014
Bisoprolol	0.097 ± 0.010	0.266 ± 0.011
Mesenteric artery		
Placebo	0.125 ± 0.021	0.131 ± 0.013
Bisoprolol	0.089 ± 0.008**	0.118 ± 0.009
Renal artery		
Placebo	0.081 ± 0.009	0.163 ± 0.005
Bisoprolol	0.075 ± 0.014	0.141 ± 0.004*

Values are mean ± 1 standard deviation.

P *values:* * *<.05;* ** *<.001 (placebo* v *bisoprolol).*

Number of animals, see Table 1.

Treatment had a significant effect on the thickness of two of the five arterial segments studied (Table 2). Thus, at the site of the thoracic aorta and the renal artery, bisoprolol-treated rats showed lower values of medial cross-sectional area: 0.947 ± 0.03 mm^2 *v* 1.078 ± 0.02 mm^2 ($P < .05$) for thoracic aorta, and 0.141 ± 0.004 mm^2 *v* 0.163 ± 0.005 mm^2 ($p < .05$) for the renal artery. In the other arterial segments, no significant difference was observed.

DISCUSSION

In recent years, cardiovascular structures in rats have been widely studied following antihypertensive drug treatment. For the study of structural changes in the arterial wall, perfusion fixation techniques are considered the method of choice to obtain morphometric data on vascular tissue.[10–12] In the present study, the observed values of media cross-sectional areas in untreated SHR, whether younger or older, were similar to those previously described in the literature.[2,3,5] Nevertheless, following chronic β_1-blockade, two unexpected findings were observed. First, whereas selective β-blockade is known to act predominantly on the heart, a significant arterial antihypertrophic effect was observed. Second, whereas β-blocking agents are known to have a well-established negative inotropic effect, bisoprolol decreased substantially the development of cardiovascular complications in older SHR through a decrease in the incidence of cardiac failure.

As selective β-blockade is known to cause predominant effects on the heart and not on the vessels,[13,14] it seems likely that the structural arterial changes produced by bisoprolol may be directly related to the blood pressure reduction observed in SHR following 2 months of treatment. In the literature, several lines of evidence indicate that arterial hypertrophy represents a response to increased blood pressure and wall stress[15–17]: i) a high degree of correlation may be observed between the level of blood pressure and structural arterial changes in a variety of hypertensive models; ii) the development of smooth muscle hypertrophy in aortas of SHR occurs predominantly after

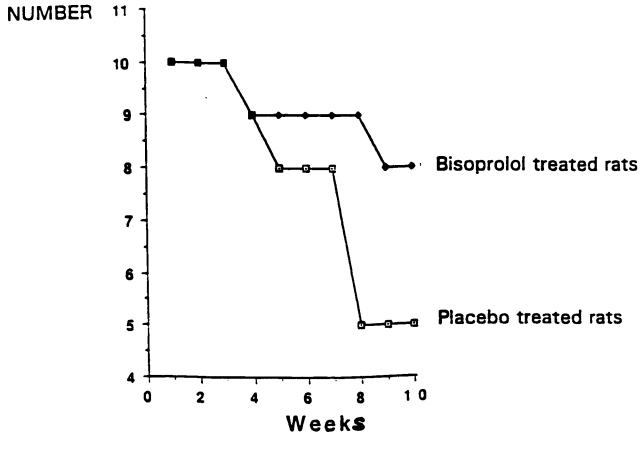

FIGURE 2. *Older animals. Length of life survival in the Bisoprolol- and the placebo-treated animals as function of time.*

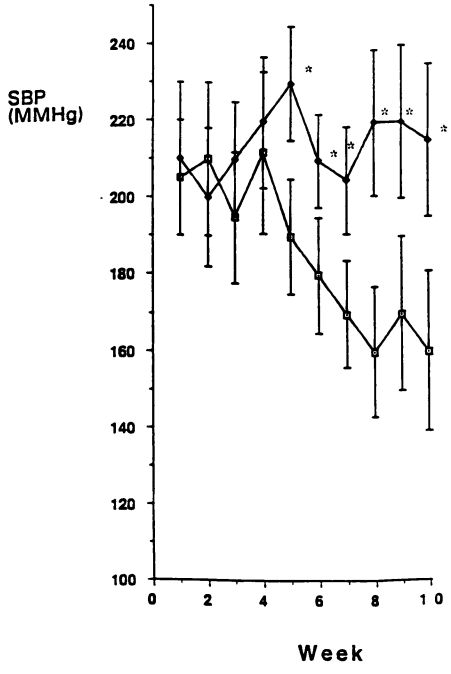

FIGURE 3. *Older animals. Systolic blood pressure (SBP) evaluated with the tail-cuff method during the treatment period.* —⊡—, *placebo;* —♦—, *bisoprolol. Values are mean ± SD.* *P < .01.

blood pressure has increased to its maximal level; and iii) normalization of blood pressure in SHR with antihypertensive drug treatment is effective in preventing further development of arterial smooth muscle hypertrophy, as well as in reversing some of the hypertrophic changes that have already occurred. However, in the present study, several findings are in clear contrast to this general interpretation. First, in younger animals treatment with bisoprolol had a moderate antihypertensive effect. Second, in older animals, bisoprolol-treated rats showed lower values of arterial cross-sectional area despite even higher values of blood pressure as compared with the placebo-treated animals. Third, both in younger and older animals, the vascular responses were quite heterogeneous, depending on age and the regions involved. In younger animals, arterial hypertrophy was substantially reduced at the site of the aorta and the mesenteric artery, whereas the carotid and the renal arteries were not affected. In older animals, arterial hypertrophy was reduced only at the site of the thoracic aorta and the renal artery. Therefore, for the same operating mean arterial pressure following drug treatment, changes in arterial structure differed in the various regions of the arterial tree.

Several arguments in the literature suggest that nonhemodynamic factors might play a major role in the observed antitrophic effects of bisoprolol in SHR. Recent studies have shown that a significant β_1-adrenoceptor–mediated relaxation may be observed in some segments of the arterial tree, particularly at the site of the femoral and mesenteric arteries,[18–20] but not at the site of the renal arteries.[21] Also, one of the particularities of the innervation of arteries is the change in sensitivity that occurs abruptly at the branching point of some of them[22]; in the present study, this pattern was particularly noticeable for the carotid artery. Taken together, such findings strongly suggest that nonhemodynamic factors influence greatly the structure of the arterial wall following Bisoprolol administration. In a first line of evidence, it should be noted that the vascular generation of angiotensin II, which is known to be potentially responsible for arterial hypertrophy,[23] is enhanced by stimulation of β-agonists and inhibited by propranolol.[24] On the other hand, the reduced β-adrenoceptor–mediated relaxation in SHR may be related to a number of various mechanisms. Following β-blockade, a resulting increase in the activity of α-receptors may be involved. Also, a reduced function of stimulatory guanosine 5′-triphosphate binding protein may be responsible for the change in β-responsiveness,[25–27] independent of any abnormality in the β-receptors themselves.

One of the most interesting findings of the present study was the increase in life survival and decrease in cardiovascular complications following bisoprolol treatment in older SHR. At this point we have to mention that the duration of the follow-up was relatively short. However, one of the aims of our study was to evaluate the cardiac and arterial effects of β-blockade when treatment was started at a very late age in SHR. Longer follow-up of these rats was practically impossible due to the high mortality in the placebo group. Treatment with bisoprolol was able to partially prevent the development of heart failure in SHR at this advanced age. This can explain the paradoxically higher values of blood pressure in the drug-treated animals. Actually, the low blood pressure values in the placebo group were one of the results of the development of heart failure. The observed mortality in the placebo rats in our study was very similar to the mortality previously observed in this strain of rats at this age (between 20 and 23 months).[7] Knorr et al[7] showed that converting enzyme inhibitor and calcium entry blockers have more pronounced effects on mortality, compared with other treatments like hydralazine or Minoxidil. As the authors of this review mentioned, data with diuretics and β-blockers are insufficient or unavailable. Therefore, we believe that our study provides new data on this topic. Moreover, treatment with bisoprolol in older animals had a significant antihypertrophic effect on the heart. Actually, the most pronounced difference between the two groups of older rats was observed for the right rather than the left ventricle. Our study cannot give a definitive explanation for this difference. Nevertheless, we can suggest that in the presence of advanced heart failure there is a more pronounced alteration of the right than the left ventricle.

Recently, there has been increasing evidence that β-blocking agents have a favorable effect on the natural history of heart failure. Indeed, downregulation of β-cardiac receptor occurs during the development of heart failure and selective β-blockade can restore the function of these receptors.[28] In addition, a change in the functional activity of the myocardial inhibitory G protein may be involved.[29] However, in the literature, such studies were limited to the relationship between β-receptors and the heart and no convincing data on large vessels were reported. The reduction of heart failure development with Bisoprolol could be related to the effects of this treatment on the aortic structure. Actually, in both young and older rats, treatment had a significant effect on thoracic aorta hypertrophy. It is well known that alterations of the structural and functional parameters of the aorta can directly influence the cardiac function during hypertension.[30] Thus decrease in aortic compliance increases cardiac afterload and pulsatile stress. Therefore the observed reduction in heart fail-

ure in older rats could be explained by the aortic effects of bisoprolol. However, further studies are needed to confirm the effects of this treatment not only on aortic hypertrophy, but also on the stiffness of the aorta.

At the end of this study, it should be emphasized that some caution must be exercised in deducing the specific mechanisms involved based on the particular effects of various pharmacologic agents in vivo. This need for caution derives from the fact that blood pressure changes reflect the net effect of a large number of variables, including cardiac output, heart rate, peripheral resistance, plasma volume, and plasma ion concentrations, which could be influenced either directly or indirectly by the drugs used. Alternatively, specific drugs may have direct unknown effects on cellular growth. More studies are needed comparing the effects of different subgroups of β-blockers to obtain more information concerning the mechanisms involved. And although comparison with normotensive controls of different ages was not performed in the present study, the results provided clear evidence that the structural changes were, at least partially, not pressure related.

In conclusion, the present study was the first, to our knowledge, to demonstrate that selective chronic β-blockade produced a substantial antitrophic effect on the peripheral and central large arteries of spontaneously hypertensive rats. This effect is heterogeneous in nature. It is influenced by age and predominates in the thoracic aorta. It is even more pronounced in magnitude than the reduction in cardiac hypertrophy. Prolonged treatment in older SHR prevents heart failure and increases life survival by reducing the incidence of cardiovascular complications.

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REFERENCES

1. Sen S, Tarazi RC, Bumpuss FM.: Cardiac hypertrophy and antihypertensive therapy. Cardiovasc Res 1977; 427–433.
2. Levy BI, Salzmann JL, Devissaguet M, Safar ME: Remodeling of heart and arteries by chronic converting enzyme inhibition in spontaneously hypertensive rats. Am J Hypertens 1991;4:240S–245S.
3. Levy BI, Michel JB, Salzmann JL, et al: Arterial effects of angiotensin converting enzyme inhibition in renovascular and spontaneously hypertensive rats. J Hypertens 1988;6(suppl 3):S79–S81.
4. Carlier PG, Rorive GL: Pathogenesis and reversibility of the aortic changes in essential hypertension. J Cardiovasc Pharmacol 1988;7(suppl 2):S46–S51.
5. Lee RMKW, Smeda JS: Primary versus secondary structural changes of the blood vessels in hypertension. Can J Physiol Pharmacol 1985;63:392–401.
6. Bevan RD: Trophic effects of peripheral adrenergic nerves on vascular structure. Hypertension 1984; 6(suppl III):III-19–III-26.
7. Knorr A, Garthoff B, Kazda S, Stasch JP: Effects of different antihypertensive drug classes on survival in animal models. J Cardiovasc Pharmacol 1991;17(suppl 2):S94–S100.
8. Harting J, Becker KH, Bergmann R, Bourgois R: Pharmacodynamic profile of the selective β1-adrenoceptor antagonist bisoprolol. Drug Res 1986;36:200–208.
9. Buhring KU, Sailer H, Faro HP, et al: Pharmacokinetics and metabolism of bisoprolol-*14*C in three animal species and in humans. J Cardiovasc Pharmacol 1986;8(suppl 11):S21–S28.
10. Todd ME, Laye CG, Osborne DN: The dimensional characteristics of smooth muscle in rat blood vessels: a computer assisted analysis. Cir Res 1983;53:319–331.
11. Todd ME: Smooth muscle characteristics: a computed assisted analysis from serial sections, *in* Motta PM (ed): Electron Microscopy in Biology and Medicine VIII: Ultrastructure of Smooth Muscle. Boston, Kluwer Academic Publishers, 1990, pp 101–107.
12. Thorball N, Tranum-Jensen J: Vascular reactions to perfusion fixation. J Microsc 1983;129:123–139.
13. Rosendorff C, Susanni E, Hurwitz ML, Ross FP: Adrenergic receptors in hypertension: radioligand binding studies. J Hypertens 1985;5:571–581.
14. Fitzgerald JD: β-Adrenoceptor antagonists, *in* Van Zwieten PA (ed): Handbook of Hypertension. Vol. 3: Pharmacology of Antihypertensive Drugs. Amsterdam, Elsevier Science Publishers B.V., 1984, pp 249–306.
15. Owens GK: Influence of blood pressure on development of aortic medial smooth muscle hypertrophy in spontaneously hypertensive rats. Hypertension 1987; 9:178–187.
16. Owens GK: Differential effects of antihypertensive drug therapy on vascular smooth muscle cell hypertrophy, hyperploidy, and hyperplasia in the spontaneously hypertensive rat. Circ Res 1985;56:525–536.
17. Lichtenstein AH, Brecher P, Chobanian AV: Effects of desoxycorticosterone-salt hypertension on cell ploidy in the rat aorta. Hypertension 1986;8(suppl II):II50–II54.
18. Asano M, Aoki K, Matsuda T: Reduced β-adrenoceptor interactions of norepinephrine enhance contraction in the femoral artery from spontaneously hypertensive rats. J Pharmacol Exp Ther 1982;223:307–214.
19. O'Donnel SR, Wanstall JC: β_1 and β_2 adrenoceptor-mediated responses in preparations of pulmonary artery and aorta from young and aged rats. J Pharmacol Exp Ther 1984;228:733–738.
20. Fujimoto S, Dohi Y, Aoki K, Matsuda T: β_1 and β_2-adrenoceptor-mediated relaxation responses in peripheral arteries from spontaneously hypertensive rats at pre-hypertensive and early hypertensive stages. J Hypertens 1988;6:543–550.
21. Heesen BJ, De Mey JGR: Effects of cyclic AMP-

affecting agents on contractile reactivity of isolated mesenteric and renal resistance arteries of the rat. Br J Pharmacol 1990;101:859–864.

22. Bevan JA, Purdy RE: Variations in adrenergic innervation and contractile responses of the rabbit saphenous artery. Circ Res 32:746–751.
23. Dzau VJ: Vascular renin-angiotensin: a possible autocrine or paracrine system in control of vascular function. J Cardiovasc Pharmacol 1984;6:S377–S382.
24. Nakamaru M, Jackson EK, Inagami T: β-Adrenoceptor-mediated release of angiotensin II from mesenteric arteries. Am J Physiol 1986;250(Heart Circ Physiol 19):H144–H148.
25. Masuzawa K, Matsuda T, Asano M: Decreased arterial responsiveness to multiple cyclic AMP-generating receptor agonists in spontaneously hypertensive rats. Br J Pharmacol 1989;96:227–235.
26. Amer MS: Cyclic adenosine monophosphate and hypertension in rats. Science 1973;179:807–809.
27. Cohen ML, Berkowitz BA: Decreased vascular relaxation in hypertension. J Pharmacol Exp Ther 1976;196: 396–406.
28. Bristow MR, Hershberger RE, David Port J, et al: Beta-adrenergic pathways in non-failing and failing human ventricular myocardium. Circulation 1990;82(suppl I):I12–I25.
29. Schrader J, Baumann G, Gerlach E: Adenosine as inhibitor of myocardial effects of catecholamines. Pfluger Arch 1977;372:29–35.
30. Safar ME: Pulse pressure in essential hypertension. Clinical and therapeutic implications (editorial review). J Hypertens 1989;7:769–776.