Original Research

Time-Course of Mechanical Changes of the Rat Aorta Following Chronic Beta-Blocker Treatment

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Introduction: The mechanical properties of the aorta play an important role in arterial homeostasis and constitute a prognostic factor in cardiovascular disease. This study determined the time-course of mechanical changes of the thoracic aorta following prolonged beta (β)-blocker treatment.

Methods: Sixty-six healthy male Wistar rats were randomized to 4 groups. Group A was divided into subgroups A_1 (n=6), A_2 (n=6), and A_3 (n=6), with animals receiving only water. In groups B (n=16), C (n=16), and D (n=16), propranolol was added to the drinking water (100 mg/kg/day). Animals of groups A_1 and B, A_2 and C, and A_3 and D were sacrificed after 1, 2, and 3 months. The effect of β-blockade was assessed by heart rate changes in response to isoproterenol infusion. The thoracic aorta was excised and submitted to mechanical testing. Regression analysis was performed to evaluate the relationship between elastic modulus and stress for low (part I), physiologic (part II), and high (part III) stresses.

Results: Data from subgroups A_1, A_2, and A_3 were pooled together and were used as a control. Differences were found in the regression parameters of parts II and III between the propranolol-treated groups and controls, indicating that the aorta was stiffer in propranolol-treated rats compared to controls at physiologic stresses, and at physiologic and high strains. Changes developed progressively with the duration of treatment. No differences were found in the regression parameters of part I, indicative of non-varying elastic modulus, i.e. stiffness, at low stresses and strains.

Conclusion: Chronic blockade of β-adrenergic receptors induces changes in the mechanical properties of the thoracic aorta. Aortic stiffening in response to β-blocker treatment may be of great clinical significance.

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It is well appreciated today that the sympathetic nervous system plays a significant role in the determination of aortic wall function, through its direct effects on smooth muscle cells and by neurohumoral activation.[1,2] Knowledge of the effects of sympathetic nerves on the mechanical performance of the aorta is fundamental, because the aorta is not a simple conduit, but modulates the homeostasis of the entire cardiovascular system, as well as regulating left ventricular function and coronary blood flow.[1,2]

While the effects of sympathetic nerves on aortic function and structure have been examined,[3-7] those of β-adrenergic receptors on the elastic properties of the aortic wall are not well defined.[8-10] Therefore, the present study aimed to determine the evolution in mechanical properties of the thoracic aortic wall following prolonged β-blocker treatment in experimental animals.

Methods

Animals and propranolol treatment

Sixty-six healthy male Wistar rats, 3 months old, with a body weight of 305 ± 7 g (mean ± standard error of the mean, SEM), were

purchased from a commercial breeder and left to acclimatize for 5 days prior to the beginning of the study. They were individually housed in stainless steel cages in an air-conditioned room (19 ± 1° C, 55 ± 5% relative humidity) on a 12/12 h artificial light/dark cycle, having free access to conventional rat chow and tap water *ad libitum*. The animals were randomized to 4 groups. Group A was divided into subgroups A_1 (n=6), A_2 (n=6), and A_3 (n=6), in which the animals received only water. In groups B (n=16), C (n=16), and D (n=16), β-blockade was produced by administration of propranolol hydrochloride, 100 mg/kg/day, in their drinking water. The experimental study was approved by the ethics committee of our institution and was conducted according to the guiding principles of the American Physiological Society and Greek Presidential Decree 160/1991, issued after the 609/1986 Directive of the European Union.

Evaluation of β-blockade and tissue preparation

Animals of groups A_1 and B, A_2 and C, and A_3 and D were sacrificed 1, 2, and 3 months after the initiation of propranolol or vehicle treatment. They were sedated with intraperitoneal ketamine (90 mg/kg) and xylazine (5 mg/kg). For evaluation of the effectiveness of propranolol, the heart-rate response to isoproterenol was used. Isoproterenol was administered intravenously (0.5 μg/kg) to the anesthetized rats and heart rate was measured on ECG recordings (Dash 2000 Pro Monitoring, General Electric Healthcare, Bucks, UK). Maximum changes in heart rate in response to isoproterenol were studied in controls and propranolol-treated rats. Euthanasia was induced with an intravenous overdose of sodium pentobarbital.

The chest was opened through a median sternotomy and the aortic segment from the left subclavian artery to the diaphragm was harvested using eye surgery loupes (Heine HRP, Heine Optotechnik, Herrsching, Germany) to avoid damage to the aortic wall. A strip with longitudinal direction was prepared from the aortic segment, cleaned of adherent loose tissues, and used for mechanical studies within 2 h post-euthanasia.

Mechanical testing

The strips were submitted to mechanical study, while held in the grips of a uniaxial tensile-testing device (Vitrodyne V1000 Universal Tester, Liveco Inc., Burlington, VT, USA) and immersed in saline solution at 37° C, as described in previous studies from our laboratory.[11-13] To minimize viscoelasticity and acquire steady-state data, mechanical preconditioning, consisting of ten successive loading-unloading cycles with constant final levels of extension, was performed. The initial width and thickness of the strips were recorded optically via a laser beam micrometer (LS-3100, Keyence Corp, Osaka, Japan). The strips were subsequently subjected to another cycle, during which load-extension data were recorded with a 50 Hz sampling frequency. These exemplified the passive mechanical properties of aortic wall tissue under negligible smooth muscle tone.

Stress, T, was calculated as the ratio of tensile load exerted on the aortic strips to their initial width and thickness at zero load. Strain, ε, was calculated as the ratio of the strips' extension at each tensile load to their initial length at zero load. The inherent stiffness of aortic wall was quantified in terms of elastic modulus, M, which was calculated as the first derivative of stress with respect to strain. The experimental stress-strain data were plotted as elastic modulus-stress curves, and their three parts—corresponding to low, physiologic, and high stresses—were submitted to power and bilinear regression, as previously described by our laboratory (see Figure 1 for a representative example):[11-13]

$$\begin{aligned} M &= kT^q,\ 0 \le T \le T_{\mathrm{I}},\ \text{Part I},\\ M &= a + bT,\ T_{\mathrm{I}} \le T \le T_{\mathrm{II}},\ \text{Part II},\\ M &= c + dT,\ T_{\mathrm{II}} \le T \le T_{\mathrm{f}},\ \text{Part III} \end{aligned} \qquad (1)$$

T_{I} and T_{II} denote stress at the first and second transition points, defining the limits of the three parts, associated with strains ε_{I} and $\varepsilon_{\mathrm{II}}$, and T_{f} denotes the maximum stress applied. The regression parameters for part I are given by k and q, for part II by a and b, and for part III by c and d. Physiologically, symbols k, a, and c for parts I, II, and III may be considered as indices of the inherent stiffness of aortic wall at low, physiologic, and high stresses, respectively, independently of the applied stress level, while symbols q, b, and d are indicative of the progressive aortic stiffening under low, physiologic, and high stressing, respectively.

Statistical analysis

Normality tests were performed with the Kolmogorov-Smirnov criterion, which showed that the data concerning heart rate and mechanical parameters were representative of a normal distribution. Ac-

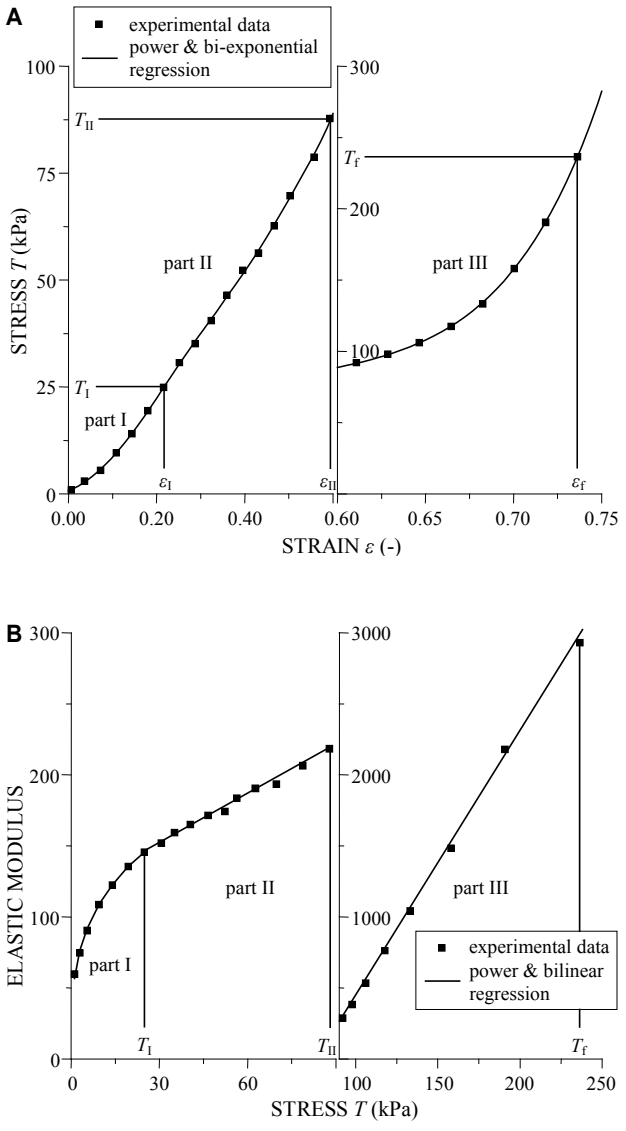

Figure 1. (A) Typical stress-strain data of the aortic wall (thoracic aorta) from an untreated rat. (B) These data were converted into elastic modulus-stress curves, yielding a nonlinear (part I) and two linear parts (II and III). Symbols T and ε with subscripts I, II, and f denote stress and strain at the first and second transition points, and maximum stress and strain.

cordingly, the results were averaged and expressed as mean ± standard error of the mean (SEM), and parametric tests were applied to assess differences among different groups. One-way analysis of variance (ANOVA), followed by a *post hoc* test (Bonferroni test), was performed in order to assess differences among the subgroups of untreated animals. It was also used for multiple comparisons among the experimental and control groups. The data were analyzed with the statistical software package SPSS v12.0 for Windows application (SPSS Inc., Chicago, IL, USA). Differences were considered to be significant at the $p<0.05$ level.

Microcal Origin v.7.5 (OriginLab® Corp., Northampton, MA, USA) was used for the non-linear and bilinear regression analysis of the three parts of elastic modulus-stress data from the thoracic aorta of propranolol-treated and non-treated rats (least-squares fitting procedure via the Levenberg-Marquardt algorithm) in terms of Eq. (1). The reproducibility of our methodology of regression analysis was studied in ten aortic specimens, using the coefficient of variation as a measure during five measurements, each performed by two independent observers. The mean intra-observer and inter-observer coefficients of variation under these conditions were 4 ± 1% and 10 ± 3%, respectively.

Results

Animals

During the study, no significant side effects or deaths related to propranolol occurred. ANOVA did not demonstrate any differences in heart rate and mechanical properties of the aorta among the three subgroups of untreated animals, which were accordingly pooled together as the control group.

Heart rate

The heart rate of anesthetized rats was significantly higher in the untreated group. In response to isoproterenol administration, the maximum increase in heart rate was appreciably reduced in the three groups of propranolol-treated rats (from 228.1 ± 7.7 to 223.4 ± 6.4/min, $p=0.4$) compared to controls (from 248.9 ± 4.9 to 325.3 ± 7.3/min, $p<0.001$), validating the sufficiency of β-blockade.

Mechanical properties

The cumulative stress-strain curves of propranolol-treated rats were shifted upwards compared with those of the untreated rats at physiologic and high levels of strain, referring to parts II and III of the curves, while this was not the case for the low-strain part (I) (Figure 2). The respective elastic modulus-strain curves of propranolol-treated rats were also displaced upwards compared with those of the untreated (control) rats at physiologic and high levels of strain, referring to parts II and III of the curves (Figure 3). The corresponding

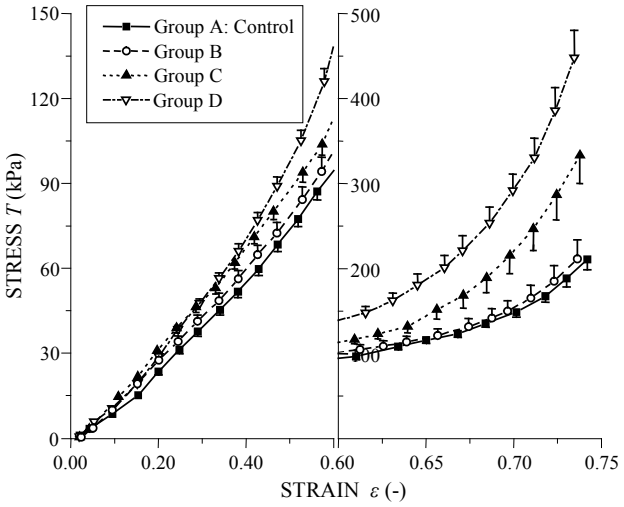

Figure 2. Stress-strain curves of the aortic wall (thoracic aorta) for the controls (Group A) and the propranolol-treated rats (Groups B, C, and D). Vertical bars denote standard error of the mean. The left panel refers to the low (part I) and physiologic (II), and the right panel to the high-strain part (III) of the curves.

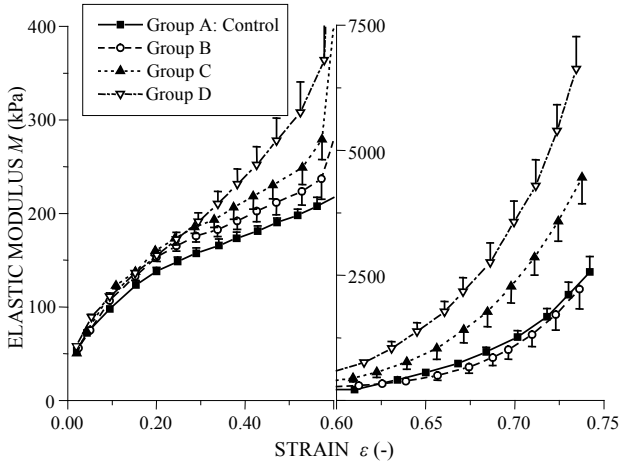

Figure 3. Elastic modulus-strain curves of the aortic wall (thoracic aorta) for the controls (Group A) and the propranolol-treated rats (Groups B, C, and D). Vertical bars denote standard error of the mean. The left panel refers to the low (part I) and the physiologic (II), and the right panel to the high-strain part (III) of the curves.

elastic modulus-stress curves of propranolol-treated rats were also displaced upwards relative to controls, but only for physiologic stress (part II) (Figure 4). The low and high-stress parts (I and III) of the curves for propranolol-treated and untreated control rats were superimposed, suggesting that the elastic modulus of the aortic wall did not differ between propranolol-treated and control rats at low and high levels of stress. Note that the differences between the curves in Figures 2 to 4 for control and propranolol-treated rats

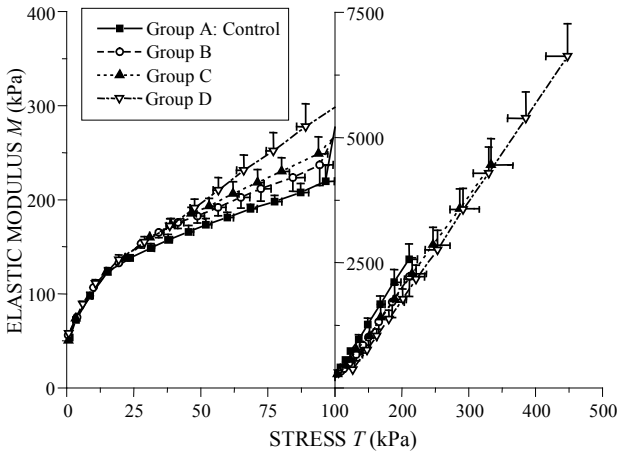

Figure 4. Elastic modulus-stress curves of the aortic wall (thoracic aorta) for the controls (Group A) and the propranolol-treated rats (Groups B, C, and D). Horizontal and vertical bars denote standard error of the mean. The left panel refers to the low (part I) and the physiologic (II), and the right panel to the high-stress part (III) of the curves.

increased progressively with the duration of treatment (i.e. from group B to group D).

Regression parameters

Comparison of the regression parameters evaluated from the elastic modulus-stress curves showed that the parameters of parts I and III did not differ between treated and untreated rats, nor did parameter *a* of part II, whereas parameter *b* gradually and significantly increased in propranolol-treated rats (Table 1). As regards the parameters of the transition points, significantly higher strain ε_I, and stresses T_I and T_{II}, but lower strain ε_{II} were found in propranolol-treated rats compared with controls. The experimental curves and the regression parameters characterizing those curves indicated that the thoracic aorta of propranolol-treated rats became progressively stiffer with the duration of treatment than that of untreated control rats at physiologic stresses, and at physiologic and high strains.

Discussion

To the best of our knowledge, the present investigation is the first to assess the *in vitro* mechanical properties of the aortic wall in response to chronic β-blocker administration in an experimental animal model. The major effect of prolonged propranolol treatment was an increase in the passive stiffness of the aortic wall at physiologic and high strains, and at physiologic stresses.

Table 1. Effect of chronic treatment with propranolol on the mechanical parameters of the aortic wall in rats.

Regression parameters		Controls (n=18)	Group B (n=16)	Group C (n=16)	Group D (n=16)
Part I	k (kPa)	65.007 ± 5.937	68.710 ± 6.500	73.770 ± 6.404	66.359 ± 6.789
	q (-)	0.381 ± 0.029	0.357 ± 0.040	0.329 ± 0.030	0.404 ± 0.025
Part II	a (kPa)	112.261 ± 7.092	115.049 ± 8.420	119.488 ± 4.941	93.747 ± 12.110
	b (-)	1.184 ± 0.079	1.228 ± 0.132	1.446 ± 0.073	2.112 ± 0.194$^{\dagger\S\#}$
Part III	c (kPa)	-1907.603 ± 244.352	-1986.455 ± 266.566	-2059.927 ± 265.073	-1895.449 ± 281.587
	d (-)	21.725 ± 1.301	20.544 ± 2.262	21.068 ± 1.583	18.688 ± 1.970
First transition point	T_I (kPa)	26.963 ± 1.247	24.175 ± 1.869	31.207 ± 2.219	41.980 ± 3.631$^{\dagger\S\#}$
	ε_I (-)	0.212 ± 0.007	0.166 ± 0.015*	0.186 ± 0.009	0.243 ± 0.015$^{\S\|\|}$
Second transition point	T_{II} (kPa)	110.913 ± 5.565	109.300 ± 7.281	119.547 ± 3.915	140.250 ± 10.887†‡
	ε_{II} (-)	0.648 ± 0.009	0.625 ± 0.015	0.619 ± 0.009	0.605 ± 0.015*

$\{k, q\}$ – parameters of part I; $\{a, b\}$ – parameters of part II; $\{c, d\}$ – parameters of part III; $\{T_I, \varepsilon_I\}$ – stress and strain at the first transition point; $\{T_{II}, \varepsilon_{II}\}$ – stress and strain at the second transition point; n – number of specimens.
*p<0.05, †p<0.01 vs. control; ‡p<0.05, §p<0.01 vs. group B; ‖p<0.05, #p<0.01 vs. group C.

Consideration of findings

Prolonged treatment with propranolol produced a significant decrease in heart rate in anesthetized rats, in agreement with other studies that demonstrated a 15% decrease in heart rate in conscious rats given daily doses of 20-100 mg/kg.[14-18] As observed in previous reports,[16,17,19] and verified by the effect of isoproterenol administration on heart rate, propranolol treatment at 100 mg/kg per day produced sufficient blockade of β-adrenergic receptors.[20]

The passive *in vitro* mechanical properties of the thoracic aorta changed significantly in response to long-term propranolol treatment, with the vessel suffering major stiffening. Mechanical testing demonstrated an increased elastic modulus, i.e. stiffness, of the thoracic aorta in propranolol-treated rats at physiologic levels of stress, and at physiologic and high levels of strain, which in view of Laplace's law correspond to physiologic and high aortic pressures.

Previously, only the short-term effect of β-adrenergic blockade on the aortic mechanics of healthy and Marfan subjects has been examined and the results have been conflicting.[8,9] Considering the results relating only to healthy subjects, a significant reduction in blood pressure following β-blocker therapy was reported in both studies, yet aortic distensibility and pulse wave velocity were unchanged in one study,[8] while in the other study[9] aortic distensibility and stiffness were increased and decreased, respectively, in response to the lowering of arterial pressure.

Even less information is available concerning the chronic influence of β-blockade on aortic mechanics. A decrease in distensibility of the abdominal aorta at a given level of distending aortic pressure has been previously documented in rats following a 3-month period of sympathetic denervation with guanethidine,[4] consistent with the increased elastic modulus reported by us. Care should, however, be exercised in comparing *in vivo* distensibility with the passive elastic modulus determined in the present study, because the latter is a stiffness index relating to the passive properties of aortic tissue, independent of vessel geometry, while the former is dependent on both the geometry and intrinsic mechanical properties of the vessel, including its active properties, i.e. the vascular smooth muscle tone.

The decreased distensibility of the abdominal aortic wall after sympathectomy with guanethidine was previously ascribed to decreased elastin content of the vessel wall.[4] No change in collagen and smooth muscle cell contents was observed, in contrast to the results of another study,[5] which reported that rabbits and rats chemically sympathectomized with 6-hydroxydopamine for 8 weeks had significantly higher collagen but lower smooth muscle cell content, together with pronounced abnormalities in the elastic tissue, in both the thoracic and abdominal aorta.

Clinical implications

Previous studies have shown that therapy with β-adrenergic blockers reduces the rate of aortic dilatation.[21-24] In cases where β-blocker therapy is contraindicated or not tolerated, calcium-channel blockers or angiotensin-converting enzyme inhibitors are used to prevent aortic dilatation.[25-27]

The hemodynamic effects of β-blockade have long been employed in the treatment of aortic dissection.[28] Long-term β-blockade may thus protect against aortic

aneurysm expansion by minimizing hemodynamic stresses on the aortic wall. Studies have shown that the low rate of abdominal aortic aneurysm expansion among patients receiving therapy with β-blockers was not associated with a decrease in mean systolic or diastolic arterial pressure.[29-31] Results of other investigations suggest that specific β-blockers may interact metabolically with aortic tissue.[32-34] Propranolol prevents aortic aneurysm formation in turkeys fed β-aminoproprionitrile,[32] this drug-mediated effect being independent of its heart rate, blood pressure, or dp/dt-lowering effects.[33] Further evidence indicates that propranolol directly increases aortic tensile strength by stimulating lysyl oxidase activity and promoting collagen and elastin cross-linking,[34] in accordance with the increased aortic stiffness disclosed in this study. Thus, the effect of propranolol in turkeys fed β-aminoproprionitrile may depend on direct interaction with β2-receptors located in non-cardiac vascular tissues. Along these lines, we may speculate that potential mechanisms for the aortic stiffening found in the present study in response to propranolol administration could be the hemodynamic effects of β-blockers and/or the direct metabolic effects of propranolol on the aortic wall.

Aortic stiffening has been previously reported in the elderly,[35] in patients with arterial hypertension,[36] diabetes mellitus,[37,38] hyperthyroidism,[39] heart failure,[40] and in smokers.[41,42] It is also an independent predictor of all-cause and cardiovascular mortality in patients with essential hypertension[43] and with end-stage renal disease.[44] Among its adverse pathophysiological sequelae is the decreased diastolic and the increased systolic and pulse pressure, due to the loss of buffering function and the higher pulse wave velocity.[1,2] Disappearance of the diastolic wave reduces myocardial perfusion, whereas augmentation of pulse pressure leads to cardiac pressure overload and hypertrophy and to increased diastolic-systolic expansion of peripheral arteries, promoting the development of vascular damage.

It is hypothesized that, when patients are treated with β-blockers for a long period of time, their aortic wall undergoes significant stiffening and structural remodeling, but confirmation will require clinical studies that will determine in normotensive and hypertensive humans the long-term effects of β-blockers on *in vivo* aortic mechanics, and histological and mechanical studies that will define the time course of changes in the mechanical and structural remodeling of the vessel. Aortic stiffening may have unfavorable implications for the cardiovascular system, yet the duration of treatment required for that process is unknown. Another important question from the standpoint of cardiovascular physiology is whether different blocking agents have varying effects on aortic structure and function, although they may induce similar overall reductions in blood pressure.

The results of the present study are of great clinical significance, since reports from recent clinical trials have suggested that therapy with β-blocking agents in patients with arterial hypertension may not be as effective in preventing cardiovascular events as angiotensin-converting enzyme inhibitors or calcium channel blockers.[45]

Study limitations

As with all experimental research, this study has several limitations. First, lack of documentation of the impact of propranolol treatment on hemodynamics, i.e. on cardiac output and aortic pressure, does not allow substantiation of the hypothesis that the adaptation of aortic design was elicited by the decreased functional load imposed by β-blockade. Second, we have previously reported[46,47] for the particular experiment of uniaxial tension that passive stiffness is determined by the content and ultrastructure of elastin at low stresses, and of both elastin and collagen at physiologic and high stresses. It is therefore suggested that changes in composition may be the chief factors leading to the presently documented mechanical remodeling of the aortic wall in response to chronic propranolol treatment, but this information requires histological examination of the aortic wall, which was not performed in this study. Third, the mechanical properties were assessed *ex vivo*, not corresponding to the optimum physiologic conditions obtained with *in vivo* studies. However, application of the experimental procedure of tensile-testing presents a number of advantages over *in vivo* methods: it measures the material properties over a wide range of stresses, not only those corresponding to the systolic-diastolic range of blood pressure during each cardiac cycle and, unlike *in vivo* methods, it is not subject to errors induced by anesthesia and iatrogenic manipulation.

Conclusions

To conclude, chronic pharmacological blockade of β-adrenergic receptors produces significant changes in the mechanical properties of the aortic wall. The aortic

wall becomes stiffer at physiologic levels of stress and at physiologic and high levels of strain, corresponding to physiologic and high levels of aortic pressure. Studies of the effect of chronic β-blockade on structure and function of the aorta will be of great clinical significance.

Acknowledgements

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