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α-Adrenergic responsiveness in rat isolated perfused heart after abdominal aortic coarctation

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Abstract

Chronic isoproterenol pre-treatment, a well-known model of compensatory hypertrophy associated with cardiac β-adrenoceptor desensitization, enhances the inotropic response to phenylephrine in rat isolated perfused hearts, supporting the hypothesis that myocardial α-adrenoceptor stimulation contributes to the maintenance of myocardial performance in situations in which cardiac β-adrenoceptor function is compromised. To further corroborate this hypothesis, the effects of abdominal aortic coarctation on cardiac α-adrenergic responsiveness were investigated in Langendorff heart preparations. Abdominal aortic coarctation causes cardiac hypertrophy (21%) as shown by a significant increase in the ratio of ventricular dry weight to bodyweight. In preparations from hypertrophied rats, both maximum increases in left ventricular systolic pressure and heart rate elicited by isoproterenol (10^{-12} to 10^{-4} M) were significantly reduced (the isoproterenol concentration producing 50% of the maximum positive inotropic and chronotropic responses was enhanced almost 21- and 2-fold, respectively). However, the positive inotropic response to phenylephrine (10^{-12} to 10^{-4} M) remained unaffected following abdominal aortic coarctation, when compared with sham-operated rats. In preparations from both groups, phenylephrine infusion did not induce significant changes in heart rate. These results show that although abdominal aortic stenosis induced desensitization of cardiac β-adrenoceptors, it did not enhance cardiac α-adrenoceptor responsiveness. This suggests that such an enhancement depends on the experimental model used to induce cardiac hypertrophy associated with desensitization of cardiac β-adrenoceptors.

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Introduction

β-Adrenoceptors are the predominant class of adrenoceptor in the heart, mediating both positive inotropic and chronotropic responses. However, the existence of functional myocardial α_1-adrenoceptors in different cardiac preparations from several species, including humans, has been well-characterized in both biochemical and functional studies (Schumann et al 1978; Wagner & Brodde 1978; Brückner et al 1984, 1985; Aass et al 1986; Terzic et al 1993). In contrast to the effects mediated by myocardial β_1-adrenoceptor stimulation, activation of post-junctional α_1-adrenoceptors in myocardium increases contractile force with little or no change in cardiac rate (Benfey 1982). Whereas positive inotropic response to cardiac β-adrenoceptor activation is related to increased levels of cyclic AMP, cardiac α_1-adrenoceptor stimulation transduces signals principally via changes in intracellular free Ca^{2+} (Minneman 1988; Scholz 1989; Terzic et al 1993). The mode of action by which cardiac α_1-adrenoceptor stimulation induces a positive inotropic effect is,

however, not yet completely elucidated. Several mechanisms have been proposed, including: (1) an indirect increased influx of extracellular Ca^{2+} leading to prolongation of the action potential; (2) degradation of polyphosphoinositides, particularly phosphatidylinositol 4,5-biphosphate (PIP2), leading to inositol-1, 4,5-triphosphate (IP3) and 1,2-diacylglycerol (DAG) formation. IP3 induces Ca^{2+} influx, which, together with DAG, activates protein kinase C (Minneman 1988; Scholz 1989; Kaku et al 1991); and (3) an increase in myofibrillar responsiveness to Ca^{2+} (for review see Terzic et al 1993). The relative contribution of these proposed mechanisms is still under investigation.

The precise role of α_1-adrenoceptor stimulation in myocardial contractility is not yet clear. Under normal conditions, β_1-adrenoceptor-mediated responses predominate over those elicited by α_1-adrenoceptors. However, changes in density of α_1-adrenoceptors have been reported under certain experimental and pathological conditions. For instance, whereas it remained unchanged in hypertensive animals (Limas & Limas 1987; Mertens et al 1992), the number of myocardial α_1-adrenoceptors was reduced in animals with experimentally-induced diabetes mellitus (Tanaka et al 1992). However, α_1-adrenoceptor density in myocardium increased following chronic treatment of rats with the β-adrenoceptor antagonist, propranolol (Mügge et al 1985; Steinkraus et al 1989), a condition where inotropic responsiveness to β_1-adrenoceptor activation is reduced (Mügge et al 1985). Using pre-treatment with isoproterenol (ISO; 40 μg kg^{-1} daily for 3 days), a well-known model of compensatory hypertrophy associated with cardiac β-adrenoceptor desensitization, Butterfield & Chess-Williams (1993) showed that responsiveness to α_1-adrenoceptor stimulation is enhanced in rat papillary muscle preparations. Recently, we showed that long-term (10 days) pre-treatment with ISO induced the expected cardiac β-adrenoceptor desensitization while simultaneously enhancing the positive inotropic responsiveness to phenylephrine in Langendorff heart preparations (Silva et al 2001). These results extend previous findings that myocardial α_1-adrenoceptor stimulation may contribute to the maintenance of myocardial performance in situations in which cardiac β-adrenoceptor function is impaired (Brückner et al 1985; Osnes et al 1985; Homcy et al 1991; Butterfield & Chess-Williams 1993). To further corroborate this hypothesis, the present study investigated the effects of abdominal aortic coarctation on inotropic responsiveness to α-adrenoceptor stimulation in rat isolated perfused heart according to the Langendorff method.

Materials and Methods

Drugs

(−)-Isoproterenol hydrochloride and (−)-phenylephrine hydrochloride (PHE) were purchased from Sigma Chemical Co. (St Louis, MO) and were dissolved in saline just before use. Solutions were freshly made each day and kept in the dark. Heparin (Laboratoires Léo S. A., Montigny-le-Bretonneux, France) was used as the commercially available injectable solution. Penicillin G benzathine salt (Lafepe, Recife, PE, Brazil) was dissolved in sterile isotonic saline solution.

Abdominal aortic coarctation

Male Wistar rats, 220–240 g, were cared for in accordance with the Guide for the Care and Use of Laboratory Animals, published by the US National Institutes of Health (publication no 85-23, revised 1996). They were kept under conditions of constant temperature (23 ± 2°C) with a standard 12-h light–dark cycle, and had free access to food and water. Abdominal aortic coarctation was performed under general anaesthesia with ether and under aseptic conditions. The abdominal aorta just below the diaphragm was surgically isolated above the renal vessels and coarcted using the ligature-needle technique of Morkin & Ashford (1968). Sham-operated rats underwent all surgical procedures except aortic stenosis. Immediately after surgery, rats received an intramuscular injection of penicillin (24000 IU). This treatment with antibiotic was repeated every second day during the 2-week period after surgery. Bodyweight was measured every second day after aortic coarctation or sham operation. Functional in-vitro experiments were performed 40 days after aortic coarctation or sham operation.

Perfusion model

At the time of experiments, rats were stunned, intravenously heparinized (1000 IU kg^{-1}) and killed by cervical dislocation. After thoracotomy, hearts were quickly excised and arrested in ice-cold perfusion medium. After removal of lung and fat tissue, hearts were immediately mounted and perfused according to the Langendorff technique at a constant perfusion pressure of 80 mmHg. Retrograde perfusion of the aorta was achieved with filtered (0.65-μm; Millipore), modified Krebs-Henseleit solution (pH 7.4) containing (mM): NaCl 129, KCl 5.6, $MgCl_2$ 1.25, $NaHCO_3$ 21, $CaCl_2$ 1.25 and NaH_2PO_4 1.2. Glucose (10 mM) was added as a substrate. Sodium pyruvate (2 mM) was added as a co-

substrate to preserve myocardial performance during the 120-min perfusion period (Van Bilsen et al 1988). This buffer was continuously aerated with 5% CO_2 in oxygen and maintained at 37°C. Under these conditions, the hearts beat spontaneously.

Recording of cardiac parameters

Left ventricular systolic pressure (LVSP) was measured through a cannulated, water-filled latex balloon inserted through the atrium into the left ventricle, and connected by a polyethylene catheter to a blood pressure transducer, which in turn was connected to a Gilson model 5/6 H polygraph (Gilson Medical Electronics Inc., Middletown, WI). Heart rate (HR) was calculated from LVSP tracing. The collapsed balloon attached to the transducer was secured in place and filled with water to a volume that produced a left ventricular diastolic pressure (LVDP) of approximately 10 mmHg.

Experimental protocol

After perfusing the hearts for an equilibration period of 30 min, baseline measurements of LVSP, LVDP and HR were made, and the following experiments were performed in preparations from both aortic-coarcted and sham-operated rats. In the first series of experiments, a concentration–effect curve was made with increasing bolus (0.1 mL) concentrations of ISO, over the range of 10^{-12} to 10^{-4} M. ISO boluses were separated by 5–10-min intervals, allowing LVSP and HR values to return to their respective baseline levels, as established during the equilibration period. In the second series of experiments, maximum percentage changes in LVSP and HR to bolus (0.1 mL) concentrations of PHE (10^{-12} to 10^{-4} M) were determined. Only one concentration of PHE could be achieved in each preparation. In all experiments, maximum changes in LVSP and HR evoked by ISO or PHE in both sham-operated and aortic-coarcted rats occurred within 15 s after drug infusion.

Determination of cardiac hypertrophy

Cardiac hypertrophy was determined in another set of aortic-coarcted or sham-operated rats. Animals were killed by cervical dislocation and the hearts excised. Large blood vessels and atria were removed and ventricles were rinsed with saline and blotted with filter paper. They were weighed, dried for 48 h in a desiccator at 70°C and reweighed (Knufman et al 1987). The dry ventricular weight to bodyweight ratio was used as an index of cardiac hypertrophy.

Determination of pD_2

Concentration–effect curves were obtained by plotting the maximum increases in LVSP and HR (expressed as percentage of baseline values) as a function of the negative logarithm of drug concentration. The pD_2 value was defined as the negative logarithm of agonist concentration (M) producing 50% of the maximum effect (EC50). In experiments with ISO, this value was determined graphically in each individual concentration–effect curve. The geometric mean pD_2 was calculated by averaging the pD_2 values of each concentration–effect curve. In experiments with PHE, since only one concentration of this agonist was tested in each preparation, only the apparent geometric pD_2 was determined from the mean concentration–effect curve.

Statistical analysis

All the results are expressed as means$\pm$s.e.m. The significance ($P < 0.05$) of the results was assessed using unpaired or paired Student's *t*-tests, Mann-Whitney U-tests, and one-way (groups or concentrations) or two-way (treatment $\times$ concentrations) analysis of variance.

Results

Effects of abdominal aortic coarctation pretreatment on bodyweight and heart weight

An average of 25% of animals submitted to abdominal aortic stenosis died within 2 weeks after surgery. Abdominal aortic coarctation did not affect bodyweight, but significantly ($P < 0.001$, unpaired Student's *t*-test) increased both ventricular wet and dry weights (Table 1). The procedure resulted in myocardial hypertrophy

Table 1 Effects of abdominal aortic coarctation on heart and bodyweight.

	Sham-operated rats	Aortic-coarcted rats
Initial bodyweight (g)	236$\pm$5	240$\pm$4
Final bodyweight (g)	347$\pm$11†	361$\pm$9†
Ventricular wet weight (mg)	948$\pm$12	1040$\pm$5*
Ventricular dry weight (mg)	199$\pm$7	250$\pm$12**
Ventricular dry weight/ bodyweight (mg g^{-1})	0.56$\pm$0.01	0.67$\pm$0.04**

Values are means$\pm$s.e.m. (n = 11 rats per group). †$P < 0.001$ vs initial bodyweight of sham-operated or aortic-coarcted rats (paired Student's *t*-test). *$P < 0.05$, **$P < 0.001$ vs sham-operated rats (unpaired Student's *t*-test).

(21%) as shown by the significant ($P < 0.001$, unpaired Student's t-test) increase in the ratio of ventricular dry weight to final bodyweight (Table 1).

Effects of abdominal aortic coarctation on LVSP and HR values and their changes in response to increasing concentrations of ISO (Series 1)

In this series of experiments, baseline LVDP values (average 10 mmHg) in Langendorff preparations from aortic-coarcted rats were of the same order of magnitude as those recorded in control preparations (i.e. from sham-operated rats), and remained stable throughout the entire recording period (data not shown). Baseline values of LVSP, however, were significantly higher in aortic-coarcted (81.0±1.5 mmHg, n = 6) than in sham-operated (72±2 mmHg, n = 6) rat hearts ($P < 0.001$, unpaired Student's t-test). In contrast, baseline HR values in aortic-coarcted rats (235±5 beats min^{-1}) were of the same order of magnitude ($P > 0.05$, unpaired Student's t-test) as those in control rats (239±7 beats min^{-1}). In both groups, baseline values of LVSP and HR remained stable throughout the experimental period ($P > 0.05$, one-way analysis of variance).

In preparations from sham-operated rats, ISO infusion evoked the expected concentration-dependent increase in LVSP and HR (Figure 1; $P < 0.001$, one-way analysis of variance). Both effects were significant at concentrations of 10^{-12} and 10^{-10} M, respectively ($P < 0.01$, paired Student's t-test with respect to baseline values). In hearts from aortic-coarcted rats, the same treatment also increased LVSP and HR in a concentration-related manner (Figure 1; $P < 0.001$, one-way analysis of variance). These responses became significant at a concentration of 10^{-10} M ($P < 0.01$, paired Student's t-test) and were significantly diminished over the whole concentration range used (except at 10^{-12} M with respect to HR response), when compared with control rats (Figure 1; $P < 0.05$, Mann-Whitney U-test). The curves for both ISO-induced maximum percentage increase in LVSP and HR were shifted downward after abdominal aortic coarctation (Figure 1; $P < 0.001$, two-way analysis of variance). In preparations from sham-operated and aortic-coarcted rats, the pD_2 values were 8.30±0.25 and 6.97±0.22 for LVSP, and 8.60±0.43 and 8.36±0.54 for HR, respectively, yielding EC50 ratios of aortic coarctation to sham operation of 21.3 and 1.8 for LVSP and HR, respectively.

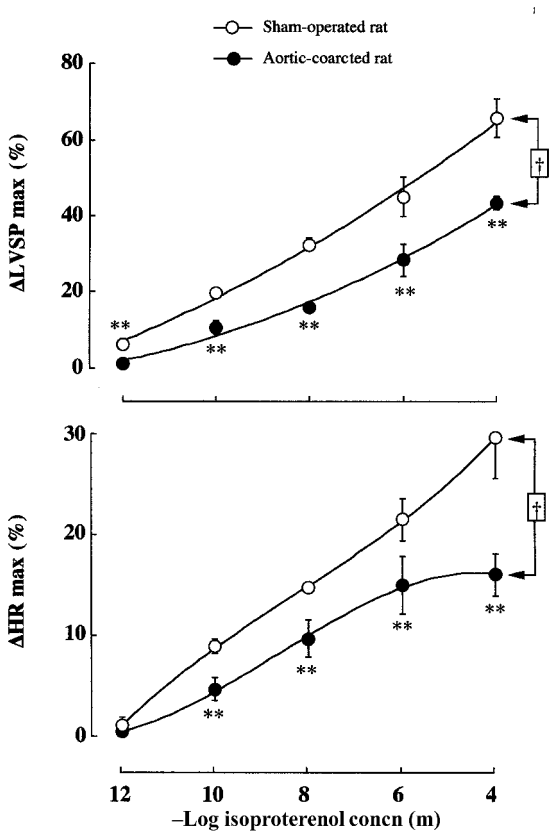

Figure 1 Maximum percentage increase in left ventricle systolic pressure (LVSP) and heart rate (HR) during infusion of increasing bolus concentrations of isoproterenol (10^{-12} to 10^{-4} M) in isolated perfused hearts from sham-operated and aortic-coarcted rats. Vertical bars indicate s.e.m. (n = 6 rats per group). The curves of the isoproterenol-induced increase in LVSP and HR were shifted downward after abdominal aortic coarctation (†$P < 0.001$, two-way analysis of variance). **$P < 0.01$ vs pre-injection values (paired Students t-test).

Effects of abdominal aortic coarctation on LVSP and HR responses to PHE at increasing concentrations (Series 2)

In this series of experiments, baseline LVDP values in preparations from aortic-coarcted rats were also of the same order of magnitude as those recorded in control preparations, and remained stable throughout the entire recording period (data not shown). As shown in Series 1, baseline values of LVSP recorded in the present series of experiments were significantly higher in aortic-coarcted (80±2 mmHg, n = 6) than in sham-operated (75±1 mmHg, n = 6) rat hearts ($P < 0.001$, unpaired Student's t-test). However, baseline values of HR were of the same order of magnitude, irrespective of whether the animal was submitted to abdominal aortic coarctation (223±7 and 231±5 beats min^{-1}, respectively). In both groups, baseline values of LVSP and HR remained stable throughout the whole recording period ($P > 0.05$, one-way analysis of variance). Finally, neither

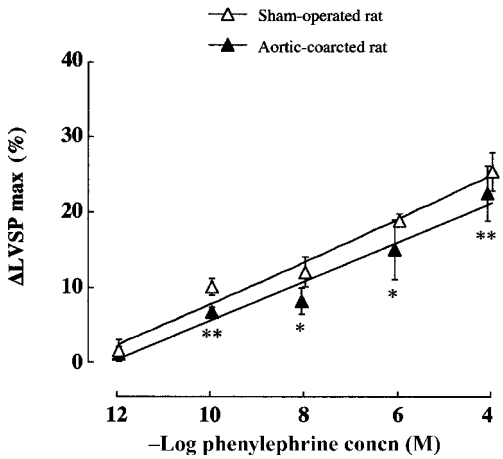

Figure 2 Maximum percentage increase in left ventricular systolic pressure (LVSP) during infusion of increasing bolus concentrations of phenylephrine (10^{-12} to 10^{-4} M) in isolated, perfused hearts from sham-operated and aortic-coarcted rats. Vertical bars indicate s.e.m. (n = 6 rats per group). The curve of the phenylephrine-induced increase in LVSP in aortic-coarcted rats was not significantly different from that in sham-operated controls ($P > 0.05$, two-way analysis of variance). $*P < 0.05$, $**P < 0.01$ vs pre-injection values (paired students t-test).

baseline parameter varied significantly from those in Series 1 ($P > 0.05$, unpaired Student's t-test).

In preparations from both sham-operated and aortic-coarcted rats, PHE infusion induced a concentration-dependent increase in LVSP (Figure 2; $P < 0.001$, one-way analysis of variance), an effect that was significant at a concentration of 10^{-10} M ($P < 0.01$, paired Student's t-test). However, PHE-induced maximum percentage increases in LVSP in aortic-coarcted rats were not statistically different from those of sham-operated rats (Figure 2; $P > 0.05$, two-way analysis of variance). In sham-operated and aortic-coarcted rats, the apparent pD_2 values were 8.05 and 7.41, respectively. In preparations from both groups, PHE infusion evoked non-significant ($P > 0.05$; paired Student's t-test) changes in HR over the whole concentration range used (data not shown). In the presence of 10^{-7} M propranolol in the medium, no significant differences ($P > 0.05$, two-way analysis of variance) in the inotropic responsiveness to PHE were found between sham-operated and aortic-coarcted rats (data not shown).

Discussion

Abdominal aortic coarctation induced no changes in rat bodyweight, but did induce a true myocardial hypertrophy as shown by the significant increase in the ratio of ventricular dry weight to final bodyweight. However, the magnitude (21%) of this cardiac hypertrophy was smaller than that reported by others (Foster et al 1991; Mertens et al 1993; Muders et al 1995; Akers et al 2000) using the same preparation. Such a discrepancy may be owing to differences in the severity or duration of pressure overload or in the rat strain used.

It is known that activation of myocardial β-adrenoceptors, both by neurally released norepinephrine and by epinephrine released from the adrenal glands, results in both positive inotropic and chronotropic responses (Kaumann 1989). The current study shows that abdominal aortic coarctation decreased responsiveness to a β-adrenoceptor-mediated increase in LVSP and HR. This loss of responsiveness or desensitization is reflected in the increase of about 21- and 2-fold in the EC50 of ISO-induced changes in LVSP and HR, respectively. Such functional changes are in good agreement with data previously reported (Chevalier et al 1989; Foster et al 1991; Akers et al 2000). Hence, in view of its morphological and functional effects, the rat abdominal aortic coarctation model used in the present study appears to be valid. The present investigation did not attempt to assess the mechanism underlying the observed loss in functional responsiveness to β-adrenergic stimulation after abdominal aortic coarctation. This mechanism, which is not completely clear, may involve either change in number or affinity of cardiac β-adrenoceptors, or alterations in post-receptor events. Several investigators have reported that cardiac β-adrenoceptor density was not altered in the rat aortic coarctation model of cardiac pressure overload (Cervoni et al 1981; Chevalier et al 1989; Mansier et al 1991, 1993). In a study in hypertrophied hearts of rats subjected to aortic coarctation, Foster et al (1991) showed that reduced inotropic responsiveness to ISO is related to post-receptor mechanisms including alterations to cAMP metabolism rather than alterations in cardiac β-adrenoceptor density. In a recent study, Akers et al (2000) showed that despite reduced inotropic responsiveness to ISO in the isolated perfused heart, cardiac β-adrenergic receptor density and the relative β_1- to β_2-receptor subtype distribution were not altered after pressure overload. The authors suggested that rather than receptor down-regulation, desensitization of the cardiac β-adrenergic receptor may be an earlier response to elevations in systemic and cardiac sympathetic nerve activity observed after pressure overload.

Chronic pre-treatment with ISO was shown to reduce positive inotropic responsiveness to ISO in isolated rat hearts through a mechanism involving functional uncoupling of the β-adrenoceptor from the adenylate

cyclase and reduction of cardiac β-adrenoceptor density (Yamaguchi et al 1981; Chang et al 1982; Harden 1983; Sibley & Lefkowitz 1985, 1987; Nanoff et al 1989). Recently, we showed that long-term pre-treatment with ISO induced the expected functional cardiac β-adrenoceptor desensitization while simultaneously enhancing the positive inotropic responsiveness to PHE in Langendorff heart preparations (Silva et al 2001). These results extended previous findings suggesting that myocardial α_1-adrenoceptor stimulation may contribute to the maintenance of myocardial performance in situations in which cardiac β-adrenoceptor function is impaired (Brückner et al 1985; Osnes et al 1985; Homcy et al 1991; Butterfield & Chess-Williams 1993). By using the rat aortic coarctation model of cardiac pressure overload, our purpose was to further corroborate this hypothesis. In Langendorff hearts from both sham-operated and aortic-coarcted rats, PHE infusion evoked a concentration-dependent increase in LVSP without significantly affecting the cardiac rate. However, the positive inotropic response to PHE was of the same order of magnitude, irrespective of whether the rat was submitted to abdominal aortic coarctation. Similar results have also been observed when LVSP responses to PHE were studied in the presence of 10^{-7} M propranolol in the medium, in order to rule out any influence of β-adrenoceptor stimulation (data not shown). Our results are in agreement with those of Mertens et al (1993), but they contrast with a previous report by Foster et al (1991) showing that inotropic response to PHE was instead reduced by about 30% 3 weeks after aortic coarctation. Thus, although abdominal aortic coarctation induces cardiac β-adrenoceptor desensitization, it did not show any enhancement in cardiac α-adrenoceptor responsiveness, at least under our experimental conditions.

The reason for such a lack of enhancement is unclear at present. Nevertheless, the following explanations could be considered. First, cardiac α_1-adrenoceptor stimulation is known to utilize changes in intracellular free Ca^{2+} as its primary pathway of signal transduction (Minneman 1988; Scholz 1989). PHE, unlike other α_1-adrenoceptor agonists, also mobilizes intracellular Ca^{2+} stores. The sarcoplasmic reticulum (SR) Ca^{2+} ATPase (SERCA2) pump plays an important role in the contraction–relaxation cycle in the myocardium by regulating the intracellular Ca^{2+} concentration. Schouten et al (1990) showed that function of the SR was depressed in the hypertrophy secondary to pressure overload. Decreased SR Ca^{2+} transport function was further reported by de la Bastia et al (1990) in a rat model of ventricular pressure-overload hypertrophy. Thus, it appears that differences exist in the biochemistry of the heart remodelled by severe aortic coarctation and chronic pre-treatment with ISO, and that SR may be involved in the process of adaptation of the myocardium to increased haemodynamic load. Second, it is possible that enhanced α-adrenoceptor responsiveness occurs mainly at the earlier stages of compensated ventricular hypertrophy, as is the case for the chronic ISO pre-treatment rat model. The high mortality rate and inadequate hypertrophy response in the aortic coarctation model indicate that the animals are at decompensated heart failure stage. Recently, Aoyagi et al (1999) studied the SERCA2 promoter gene activity in two models of ventricular haemodynamic overload: DOCA-salt and aortic coarctation. They found that SERCA2 promoter gene activity was unchanged in the DOCA-salt model, indicating that the hearts in these animals were in compensated hypertrophy. However, this activity was markedly decreased in aortic-coarcted rats indicating that these animals had progressed into heart failure. By investigating mortality rate, haemodynamic and biochemical parameters, and cardiac muscle adaptations, Crandall et al (1991) have reported that cardiac pump failure occurs between 1 and 3 months after aortic coarctation. Third, changes in the myosin isozymes toward the slower form (V3) leading to a decrease in the maximum actomyosin ATPase activity have been reported in the pressure-overload hypertrophy rat model (Mercadier et al 1981) and could contribute to the present findings. However, such a hypothesis seems unlikely, since Foster et al (1991) showed that positive inotropic response to increasing perfusate Ca^{2+} concentrations was comparable in hearts of aortic-coarcted and sham-operated rats, indicating that contractile protein responsiveness to non-receptor agent stimulus is preserved in hypertrophied hearts of aortic-coarcted rats. Finally, there has been disagreement regarding the behaviour of cardiac α-adrenoceptors in hypertrophied hearts from aortic-coarcted rats. For instance, Foster et al (1991) reported that reduced inotropic responsiveness to PHE in pressure-overload hypertrophied rat hearts could be partially related to reduced cardiac α-adrenoceptor density. However, neither the affinity nor density of the cardiac α-adrenoceptors changed 2, 6 and 28 days after abdominal aortic coarctation in rats (Lai et al 1984). No difference in the absolute density of α-adrenoceptors has been observed in failing hearts when compared to the non-failing hearts (Bristow et al 1988). On the other hand, Crandall et al (1991) reported that myocardial α-adrenoceptor number was increased 1 month, but not 3 and 12 months, after aortic coarctation. These contrasting data could be related to several factors

such as differences in the severity of aortic stenosis or in the techniques of binding experiments (heart membrane preparation and choice of the radioligand).

Conclusions

In summary, this study shows that although abdominal aortic coarctation induced cardiac β-adrenoceptor desensitization, it did not enhance the positive inotropic responsiveness to PHE in Langendorff heart preparations. Thus, it seems that enhanced α-adrenoceptor responsiveness appears to be highly model-dependent and may be stage-dependent in the rat aortic coarctation model of cardiac pressure-overload. It would be highly recommended to study the inotropic responsiveness to α-adrenoceptor stimulation at different stages (10 and 20 days) of aortic coarctation. The question remains as to whether stimulation of α-adrenoceptors plays a role in the maintenance of myocardial performance in heart failure.

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