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Chronic administration of moxonidine suppresses sympathetic activation in a rat heart failure model

Roeland Van Kerckhoven [a,*], Toon A.B. van Veen [a], Frans Boomsma [b], Pramod R. Saxena [a], Regien G. Schoemaker [a]

[a] *Department of Pharmacology, Faculty of Medicine and Health Sciences, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, Netherlands*

[b] *Department of Internal Medicine I, Faculty of Medicine and Health Sciences, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, Netherlands*

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Abstract

Excessive sympathetic activity contributes to cardiovascular abnormalities, which negatively affect the prognosis of heart failure. The present study evaluated the effects of moxonidine, an imidazoline I_1 receptor agonist, on sympathetic activation and myocardial remodelling in a rat heart failure model. Rats were subjected to coronary artery ligation, and treated with moxonidine, 3 or 6 mg/kg/day, from 1 to 21 days after myocardial infarction. After 21 days, heart rate and blood pressure were measured in conscious, chronically instrumented rats. Plasma catecholamine levels were determined by high-performance liquid chromatography. Effects on post-myocardial infarction remodelling were evaluated from the ventricular weight body weight ratio and interstitial collagen deposition, measured morphometrically in the interventricular septum remote from the infarcted area. Moxonidine dose-dependently decreased myocardial infarction induced tachycardia but did not affect myocardial infarction reduced blood pressure. Plasma noradrenaline levels, which were elevated after myocardial infarction, decreased below sham-values with 6 mg/kg/day moxonidine. Ventricular weight–body weight ratio as well as interstitial collagen were significantly elevated in myocardial infarcted rats, and restored to sham values with 6 mg/kg/day moxonidine. These data suggest that moxonidine suppresses myocardial infarction induced sympathetic activation in a dose-dependent way as indicated by reduced heart rate and plasma noradrenaline levels. Furthermore, post-myocardial infarction remodelling may be attenuated at a higher dose-range of moxonidine as shown by normalisation of ventricular weight body weight ratio and interstitial collagen.

Keywords: Collagen; Heart failure; Hypertrophy; Moxonidine; (Rat); Sympathetic activation

1. Introduction

Myocardial infarction is one of the major causes of heart failure. Although activation of neurohormonal compensatory mechanisms following myocardial infarction initially may appear beneficial and adaptive to preserve blood pressure and cardiac output, excessive and prolonged sympathetic stimulation negatively affects the prognosis of heart failure (Packer, 1992; Francis, 1998). Adverse actions of high plasma catecholamine levels include trophic and toxic effects on cardiac myocytes (Rupp et al., 1994), downregulation of β_1-adrenoceptors, increased renin secretion and myocardial as well as vascular hypertrophy (Francis et al., 1993; Ceconi et al., 1998).

Recently, imidazoline I_1 receptors in the rostral ventrolateral medulla oblongata have been recognised as a new target for centrally-acting sympatholytic drugs such as moxonidine and rilmenidine (Ziegler et al., 1996; Van Zwieten, 1997). Moxonidine is used as a centrally active antihypertensive drug, which reduces sympathetic outflow and circulating levels of catecholamines (Nurminen et al., 1998). While its antihypertensive action is well charac-

* Corresponding author. Tel.: +31-10-408-7543; fax: +31-10-408-9458.

E-mail address: vankerckhoven@farma.fgg.eur.nl (R. Van Kerckhoven).

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terised in experimental and clinical studies (Luft and Mann, 1992; Kuppers et al., 1997), the potential efficacy of moxonidine in heart failure needs to be established.

The present study was carried out to investigate the effects of chronic moxonidine therapy on myocardial infarction induced sympathetic activation and its consequences for cardiac remodelling in chronically, infarcted rats. Myocardial infarction in rats has proven to be a clinically relevant model for the consequences of myocardial infarction leading to heart failure (Anversa et al., 1985a; Schoemaker et al., 1991). Twenty-one days after myocardial infarction, heart rate and blood pressure were measured in conscious, chronically instrumented rats. Plasma catecholamine levels were measured in collected arterial blood samples. Regarding the effects of moxonidine on post-myocardial infarction remodelling, cardiac hypertrophy as well as interstitial collagen in the interventricular septum were determined.

2. Materials and methods

2.1. Animals

Male Wistar rats (Harlan, Zeist, The Netherlands) weighing 270–300 g were housed in groups of 2 or 3 on a 12 h light–dark cycle with standard rat chow and water available ad libitum. The experimental protocol was approved by the University ethics committee for the use of experimental animals and conformed with the *Guide for Care and Use of Laboratoy Animals*.

2.2. Myocardial infarction

Rats were subjected to sham surgery or coronary artery ligation. Under pentobarbital anaesthesia (60 mg/kg i.p.), myocardial infarction was induced by ligation of the left anterior descending coronary artery (Fishbein et al., 1978). Briefly, after intubation of the trachea an incision was made in the skin overlying the fourth intercostal space, with the overlying muscles separated and kept aside. The animals were put on positive pressure ventilation (frequency 65–70/min, tidal volume 3 ml) and the thoracic cavity was opened by cutting the intercostal muscles. The heart was carefully pushed to the left and 6–0 silk suture was looped under the left descending coronary artery near the origin of the pulmonary artery. After returning the heart to its normal position, the suture was tied. Intercostal space was closed by pulling the ribs with 3–0 silk, the muscles were returned to their normal position and the skin incision was sutured. Sham-operated animals underwent the same surgical procedure, without the actual coronary artery ligation. Proper occlusion of the coronary artery resulted in an extensive transmural infarction comprising a major part of the left ventricular free wall, with small variations in size (Kalkman et al., 1996).

2.3. Treatment

Infarcted rats were randomised to receive subcutaneous implantation of osmotic minipumps (Alzet® 2001, ALZA Pharmaceuticals, Palo Alto, CA) filled with moxonidine. Minipumps were replaced each week under ether anaesthesia. Sham-rats and non-treated myocardial infarcted rats underwent the same anaesthesia and surgical procedure without the actual implantation of the minipumps. Moxonidine was dissolved in a 1-ml saline buffer with 20 μl HAc and adjusted to pH = 6–6.5 with NaOH to provide a final daily dose of 3 (low-dose) or 6 mg/kg (high-dose). Administration of moxonidine was started 24 h following myocardial infarction and continued until the end of the experiment at 21 days after surgery.

2.4. Heart rate and mean arterial blood pressure

At day 19 after coronary artery ligation, rats were re-anaesthetised and a catheter (PE-10 heat-sealed to PE-50) was inserted in the abdominal aorta through the femoral artery to measure mean arterial blood pressure. The heparinised saline filled catheter was tunnelled under the skin, exteriorised at the back of the neck and closed with a metal plug. The animals were housed separately and allowed to recover for another 2 days before measurements. On the experimental day, the arterial catheter was connected to a pressure transducer (Viggo-spectramed, DT-XX, Bilthoven, The Netherlands) and signal was fed into a 68B09-based microprocessor and compatible computer, sampling at 500 Hz. After 1-h stabilisation, baseline values of mean arterial blood pressure and heart rate were obtained. Heart rate was measured as the frequency of the pulsatile pressure signal.

2.5. Catecholamines

After the registration of heart rate and mean arterial blood pressure was completed, a 1 ml arterial blood sample was collected in a syringe containing 10 μl EDTA (0.1 M) and put on ice. After centrifugation (4000 rpm for 1 min), plasma was collected in prechilled tubes filled with 1.2 mg glutathione. Plasma was stored at −80°C until assay. High-performance liquid chromatography was used to measure plasma concentrations of noradrenaline, adrenaline and dopamine, as described in detail by Boomsma et al. (1993).

2.6. Cardiac hypertrophy

When the functional measurements were completed, rats were deeply anaesthetised with pentobarbital. Then, the hearts were excised, blotted dry and weighed after removal of the atria and large vessels. Cardiac hypertrophy was defined as the ratio of ventricular weight and body weight.

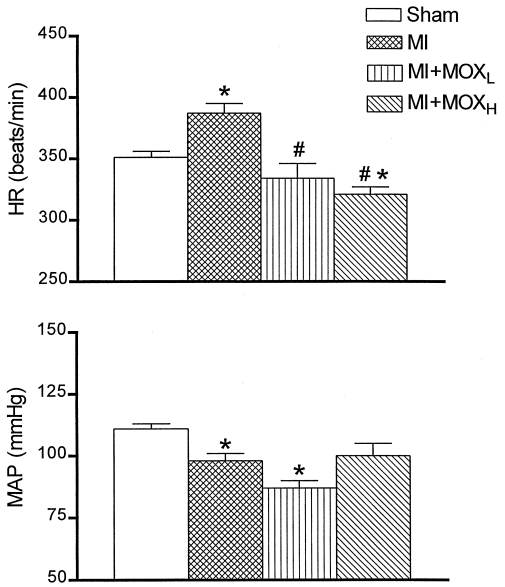

Fig. 1. Heart rate (upper panel) and mean arterial pressure (lower panel) measured in conscious rats with chronic MI. HR: heart rate; MAP: mean arterial pressure; MI: myocardial infarction; MOX_L: low-dose moxonidine (3 mg/kg/day); MOX_H: high-dose moxonidine (6 mg/kg/day). * $P < 0.01$ vs. Sham; #$P < 0.01$ vs. MI.

2.7. Interstitial collagen

Hearts were cut into four transversal slices from apex to base and fixated by perfusion with 3.6% phosphate-buffered formaldehyde for at least 24 h. After fixation, the slices were dehydrated and paraffin-embedded. Deparaffinised 5 μm thick sections were incubated for 5 min with 0.2% (w/v) aqueous phosphomolybdic acid and subsequently incubated for 45 min with 0.1% Sirius Red F3BA (C.I. 35780, Polysciences, Northampton, UK) in saturated aqueous picric acid, washed for 2 min with 0.01 M HCl, dehydrated and mounted with Entellan (Merck, Darmstadt, Germany). In the interventricular septum, remote from the infarcted area, interstitial collagen was determined as the Sirius Red positive area in 40 high power fields per heart

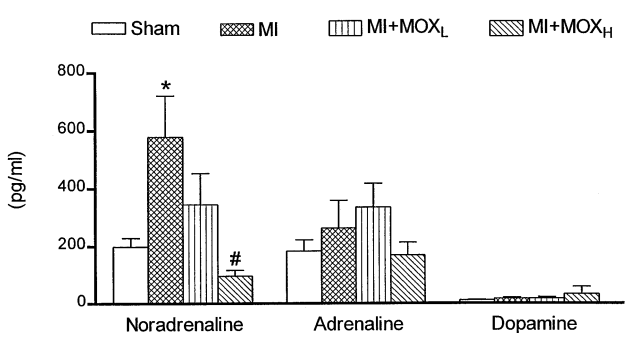

Fig. 2. Plasma concentrations of catecholamines measured in arterial blood samples obtained from resting, conscious rats. MI: myocardial infarction; MOX_L: low-dose moxonidine (3 mg/kg/day); MOX_H: high-dose moxonidine (6 mg/kg/day). * $P < 0.01$ vs. Sham; #$P < 0.01$ vs. MI.

Table 1
Body weight and ventricular weight of rats in the different experimental groups

	Sham	MI	MI + MOX_L	MI + MOX_H
n	14	12	7	7
Body weight at day 0 (g)	296 ± 5	301 ± 4	279 ± 6	297 ± 5
Body weight at day 21 (g)	333 ± 7	320 ± 10	301 ± 5	299 ± 9[a]
Ventricular weight at day 21 (mg)	1174 ± 37	1543 ± 75[a]	1410 ± 104	1076 ± 24[b]

Data are presented as means ± s.e.m. MI: myocardial infarction; MOX_L: low-dose moxonidine (3 mg/kg/day); MOX_H: high-dose moxonidine (6 mg/kg/day).
[a] $P < 0.01$ vs. Sham.
[b] $P < 0.01$ vs. MI.

(Whittaker et al., 1994; Kalkman et al., 1995). Areas that enclosed signs of replacement fibrosis or bloodvessels, were excluded from analysis.

2.8. Data analysis

All data are presented as means ± S.E.M. Data of infarcted rats were only included if the infarction comprised the major part of the left ventricular free wall, since small infarctions are found to be haemodynamically fully compensated (Pfeffer et al., 1979; Schoemaker et al., 1991).

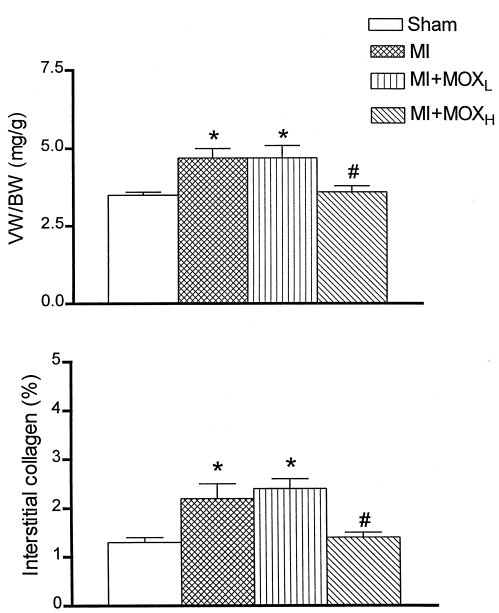

Fig. 3. Effects of moxonidine on post-MI remodelling. Cardiac hypertrophy indicated as the heart weight–body weight ratio (upper panel) and interstitial collagen expressed as percentage of total issue area (lower panel), are prsented for the different experimental groups. VW/BW: ventricular weight body weight ratio; MI: myocardial infarction; MOX_L: low-dose moxonidine (3 mg/kg/day); MOX_H: high-dose moxonidine (6 mg/kg/day). * $P < 0.01$ vs. Sham; #$P < 0.01$ vs. MI.

Estimation of infarct size by macroscopic appearance has proven to be a reliable method to recognise too small infarctions (< 20%) (Kalkman et al., 1996). Differences between groups were analysed (SigmaStat™, Jandel Scientific, Erkrath, Germany) using one-way analysis of variance (ANOVA) followed by Bonferroni's post-hoc *t*-tests for multiple group comparisons (Wallenstein et al., 1980). Differences were considered statistically significant if $P < 0.05$.

3. Results

Results comprise data from sham-rats ($n = 14$), untreated ($n = 12$), low- ($n = 7$) and high-dose ($n = 7$) moxonidine treated myocardial infarcted rats. Overall mortality following myocardial infarction was 38% and did not depend on the treatment used since death mainly occurred within the first 24 h after coronary artery ligation. No other than surgery related death were observed during the treatment period.

3.1. Heart rate and mean arterial blood pressure

As shown in Fig. 1, chronically infarcted rats showed a significantly increased heart rate compared to sham-rats, which was associated with a decreased mean arterial blood pressure. Chronic administration of low-dose moxonidine resulted in a normalisation of myocardial infarction induced tachycardia to sham-values whereas high-dose moxonidine decreased heart rate even significantly below sham-values. The observed decrease of mean arterial blood pressure in myocardial infarcted rats remained unaffected by moxonidine treatment.

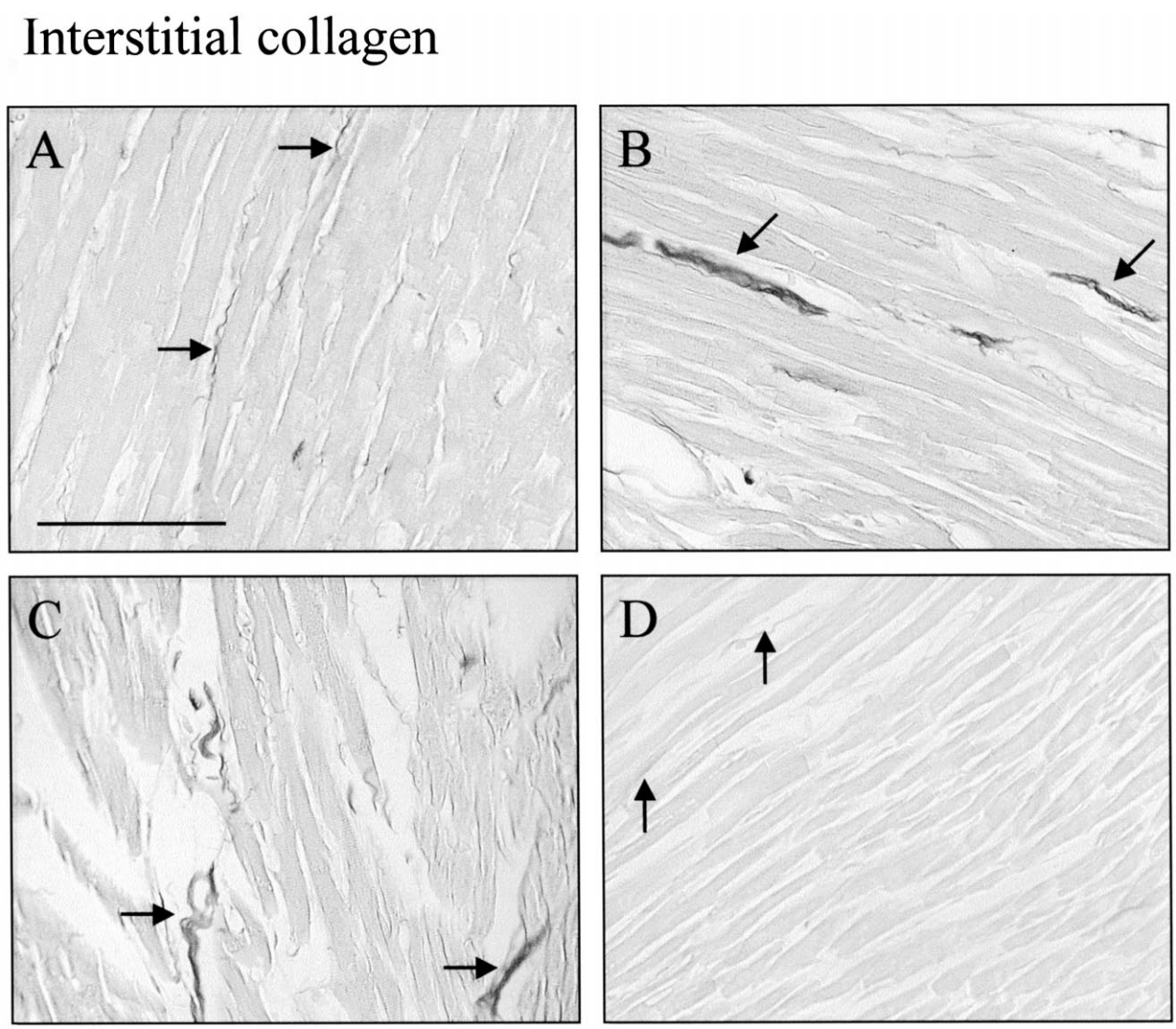

Fig. 4. Picrosirius red stained sections of intraventricular septum showing interstitial collagen (see arrows) 3 weeks after surgery. (A) sham heart, (B) untreated MI-heart, (C) low-dose moxonidine (3 mg/kg/day) treated MI-heart, (D) high-dose moxonidine (6 mg/kg/day) treated MI-heart. The bar in photomicrograph A indicates 100 μm, and accounts for all micrographs.

3.2. Catecholamines

Plasma catecholamine levels in the different experimental groups are shown in Fig. 2. Plasma noradrenaline levels were significantly elevated in untreated myocardial infarcted rats when compared to sham-rats. High-dose moxonidine reduced noradrenaline levels to about 50% the values of sham-rats. Plasma adrenaline and dopamine levels were not different between the experimental groups.

3.3. Cardiac hypertrophy

Body weight before surgery as well as ventricular weight and body weight after 21 days for the different experimental groups are summarised in Table 1. Although started at similar body weight, sham-rats gained more weight (37 ± 7 g) as compared to myocardial infarcted rats (23 ± 9 g). Low-dose moxonidine did not affect this (21 ± 9 g) but rats treated with high-dose moxonidine did not gain weight during the experimental period (1 ± 6 g). Although not accounting for all high-dose moxonidine treated infarcted rats, overall appearance of rats treated with high-dose moxonidine was less healthy as judged from their general behaviour and condition of the fur (Schoemaker and Smits, 1994; Schoemaker et al., 1996). Untreated myocardial infarcted hearts weighed significantly more than sham-operated control hearts despite replacement of the major part of the left ventricular free wall by lighter scar tissue. Ventricular weight body weight ratio was increased after myocardial infarction and significantly reduced to sham-values in myocardial infarcted rats treated with high-dose moxonidine (Fig. 3, upper panel). Low-dose moxonidine induced no changes in ventricular weight–body weight ratio compared to untreated myocardial infarcted rats.

3.4. Interstitial collagen

Photomicrographs of picrosirius red stained sections of interventricular septum containing interstitial collagen are shown in Fig. 4. Myocardial infarction induced remodelling was associated with a significant increase in interstitial collagen content of the interventricular septum compared to sham-values. Whereas interstitial collagen in low-dose moxonidine treated myocardial infarcted hearts did not differ from untreated myocardial infarcted hearts, treatment with high-dose moxonidine significantly reduced interstitial collagen compared to the values of untreated myocardial infarcted hearts. These observations were substantiated by the actual measurements as shown in the lower panel of Fig. 3.

4. Discussion

4.1. General

In recent years, both experimental studies and clinical trials have provided insight into the potential of drugs, which directly or indirectly attenuate the activity of the sympathetic nervous system such as angiotensin-converting enzyme inhibitors (Pfeffer and Stevenson, 1996; Remme, 1998) and β-adrenoceptor anatagonists (Investigators, 1991; Gu et al., 1998) to prevent progression of heart failure. The development of newer sympatholytic drugs such as moxonidine may offer an interesting alternative to peripheral β- and α-adrenoceptor blockade for the treatment of heart failure. Moxonidine has been introduced into clinical practice for the treatment of hypertension (Haxhiu et al., 1994) and shows less adverse side effects compared to first-generation centrally-acting antihypertensive drugs such as clonidine (Planitz, 1984).

In the light of these observations, the effects of chronic moxonidine therapy on sympathetic activation and post-myocardial infarction remodelling were studied in a well-established rat heart failure model (Anversa et al., 1985a,b; Schoemaker et al., 1991).

4.2. Sympathetic activation

Chronically infarcted rats manifested signs of sympathetic activation, i.e. a significantly increased heart rate accompanied by significantly elevated plasma noradrenaline levels. Accordingly, an augmented sympathetic activity associated with haemodynamic signs of heart failure, i.e. a decreased blood pressure and cardiac output, has been reported in one of our previous studies with myocardial infarcted rats (Schoemaker et al., 1998). The observed tachycardia in myocardial infarcted rats could be explained by enhanced sympathetic activity and elevated plasma noradrenaline levels, since heart rate in vivo is strongly regulated by both sympathetic nerve activity and catecholamine concentrations (Daly and Sole, 1990). Interestingly, if these myocardial infarcted hearts were isolated and perfused, heart rate is still higher than in sham-operated rats, suggesting changes in intrinsic activation of the sinus node (Schoemaker et al., 1998).

In keeping with a central reduction in sympathetic tone, myocardial infarcted rats treated with moxonidine showed a dose-dependent decrease in heart rate and plasma noradrenaline levels. A similar reduction in heart rate and plasma noradrenaline concentrations was observed in patients with severe congestive heart failure, receiving moxonidine orally for 2 to 12 weeks (Motz et al., 1998). In the present study, moxonidine therapy did not affect mean arterial blood pressure in myocardial infarcted rats. A blood pressure lowering effect of moxonidine was not likely to occur in normotensive rats. On the other hand, in spontaneously hypertensive rats long-term administration of moxonidine was shown to exhibit a dose-dependent and long-lasting reduction in blood pressure usually accompanied by a reduction in heart rate (Ziegler et al., 1996). This may be a chronic rather than an acute effect of moxonidine, since in acute experiments (data not shown) a reduced heart rate was associated with an increase in blood

pressure mediated by vascular α_2-adrenoceptors (Ernsberger, 1998).

From an energetic point of view, the lower heart rate induced by moxonidine would be beneficial to the failing heart. Infarcted hearts display a lower mechanical efficiency at rest, which is amplified by tachycardia, thereby negatively affecting the relation between myocardial oxygen demand and supply (Stewart et al., 1993). A reduction in heart rate is, independent of its origin, associated with increased capillary growth, which would greatly improve oxygenation of the heart (Hudlicka et al., 1995). Moreover, a decreased heart rate may lead to longer diastolic filling phase of the heart and improve diastolic function in heart failure. Since cardiac output and stroke volume are significantly reduced in severe heart failure, the lower heart rate with moxonidine could only be beneficial if stroke volume would be correspondingly increased to maintain cardiac output. Accordingly, as shown by Motz et al. (1998), a 10% decrease in heart rate was associated with a 20% increase in stroke volume in heart failure patients treated with oral moxonidine for 3 months.

4.3. Cardiac remodelling

Cardiac remodelling after myocardial infarction is strongly determined by cardiac loading conditions and neuroendocrine activation (Levy et al., 1990). In the rat heart failure model, large myocardial infarction evokes alterations in shape and size of the injured left ventricle and compensatory hypertrophy of the non-infarcted myocardium (Anversa et al., 1985a). In the present study, myocardial infarcted rats were characterised by an increased ventricular weight–body weight ratio at 21 days after surgery. Since body weight was not changed in these rats, compensatory cardiac hypertrophy is indicated by a rise of ventricular mass despite replacement of the major part of the left ventricular wall by lighter scar tissue. Myocardial infarcted rats treated with high-dose moxonidine had not gained weight 21 days after myocardial infarction. One explanation could be a decreased tolerance of moxonidine at higher doses since the general aspect of these rats was less healthy than other myocardial infarcted rats. Another explanation could be a reduced food intake. This suggestion is supported by data from spontaneously hypertensive rats chronically treated with 8 mg/kg/day moxonidine which also manifested loss of body weight (Ziegler et al., 1996).

In hypertensive patients (Ollivier and Christen, 1994) as well as rats (Mall et al., 1991), moxonidine was shown to be highly effective in reversing cardiac hypertrophy and protecting myocardial structure, an effect which coincided with decreased plasma noradrenaline and renin concentrations. In the present study, prevention of cardiac hypertrophy was seen in myocardial infarcted rats treated with high-dose moxonidine, whereas low-dose moxonidine had no effect on cardiac hypertrophy compared to untreated myocardial infarcted rats. The pronounced effect of high-dose moxonidine on cardiac hypertrophy is in accordance with a strong suppression of sympathetic activity, i.e. lower heart rate and plasma noradrenaline levels when compared to the lower dose.

Although regression of hypertrophy with angiotensin-converting enzyme inhibitors and β-adrenoceptor antagonists (Pfeffer et al., 1987; Pfeffer and Stevenson, 1996; Fowler, 1998) has been recognised to improve heart function and prognosis in heart failure patients (Pfeffer et al., 1992) as well as in myocardial infarcted rats, *prevention* of early hypertrophy after myocardial infarction may be regarded as compensatory and should be interfered with care. Previous experimental studies (Gay, 1990; Schoemaker et al., 1991) have clearly demonstrated that early treatment with the captopril in chronically infarcted rats resulted in prevention of hypertrophy which was associated with deterioration of in vivo haemodynamics. On the other hand in the rat myocardial infarction model, improved heart function was found with delayed captopril treatment (Schoemaker et al., 1991). Furthermore, clinical trials evaluating early intervention with angiotensin converting enzyme inhibitors in patients with acute myocardial infarction have not yielded uniform results. Whereas decreased mortality has been reported from some trials (Ambrosioni et al., 1995; Sanbe et al., 1995; GISSI-3, 1996), others did not find improved survival (Sharpe et al., 1991; Swedberg et al., 1992; Ray et al., 1993; CCS-1, 1995). Therefore, our results suggest that the high-dose moxonidine in the present study may be too high for an optimal chronic therapy.

Another event associated with post-myocardial infarction remodelling is the accumulation of interstitial (Van Krimpen et al., 1991) and perivascular collagen (Sun et al., 1994; Kalkman et al., 1995). Collagen accumulation in non-infarcted tissue has been shown to increase ventricular stiffness in myocardial infarcted rats (Raya et al., 1988). In the present study, a significant accumulation of interstitial collagen in the non-infarcted area was observed in hearts from untreated myocardial infarcted rats. High-dose moxonidine, which prevented cardiac hypertrophy, restored interstitial collagen content to sham-values, whereas low-dose moxonidine did not alter collagen content nor hypertrophy compared to untreated myocardial infarcted rats. In spontaneously hypertensive rats, moxonidine has been reported to normalise myocardial fibrosis and capillarisation to physiological levels (Mall et al., 1991). On the other hand, a too large reduction of tensile strength of the collagen network could result in aggravation of chamber dilation, as has been reported with non-steroidal anti-inflammatory drugs and steroids (Brown et al., 1983; Mannisi et al., 1987; Van Kerckhoven et al., in press).

Based on the findings of the present study, we conclude that moxonidine (3 mg/kg/day) effectively suppresses sympathetic activation after myocardial infarction without effects on cardiac hypertrophy and fibrosis. Moxonidine at

6 mg/kg/day, however, attenuated sympathetic activity even significantly below sham values, indicating the loss of a major haemodynamic regulatory system, which coincided with prevention of cardiac hypertrophy and fibrosis.

4.4. Clinical implications

Therapeutic management of heart failure should be focused on the reduction of sympathetic activation and protection of cardiac function. Research into moxonidine has contributed to the renewal of interest in centrally-acting sympatholytics and their possible benefit in the syndrome of heart failure. Preliminary clinical observations so far, suggest that the efficacy of moxonidine in the treatment of heart failure is comparable to currently used drugs such as angiotensin-converting enzyme inhibitors or β-adrenoceptor anatagonists. Chronic heart failure patients treated with oral moxonidine during a 3-month period, showed decreased plasma noradrenaline levels with an improved haemodynamic profile (Swedberg et al., 1997; Motz et al., 1998). Furthermore, the adverse side effects, which have been reported with earlier central sympatholytics, seem to be less severe.

According to the clinical observations, the findings of the present study show that moxonidine therapy effectively suppresses myocardial infarction induced sympathetic activation in conscious, chronically infarcted rats as indicated by reduced heart rate and plasma noradrenaline levels. Furthermore, post-myocardial infarction cardiac remodelling, which also is an important prognostic factor in heart failure, could also be attenuated by moxonidine. However, the dose of moxonidine in the management of heart failure needs to be chosen carefully. Therapy with a high-dose of moxonidine may lead to an unphysiologically low sympathetic tone and prevent compensatory hypertrophy, which may negatively affect prognosis of heart failure. Whether the beneficial effects of moxonidine will be associated with an improved clinical outcome in heart failure patients, needs to be further investigated.

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