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Sensitivity to ischemia of chronically infarcted rat hearts; effects of long-term captopril treatment

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Abstract

Myocardial infarction induced hypertrophy of non-infarcted myocardium, in parallel with interstitial and perivascular fibrosis and a decreased capillary density, could increase sensitivity to ischemia. The structural cardiac changes can be reversed by long-term captopril treatment. In the present study, ischemic sensitivity in relation to cardiac perfusion was studied in isolated, perfused hearts of untreated and captopril-treated infarcted rats. In chronically (8 weeks) infarcted hearts, maximal vasodilation in response to administered adenosine and nitroprusside, as well as to endogenously released vasodilators during reperfusion, was decreased, suggesting impaired cardiac perfusion. Ischemic release of purines and lactate was reduced in infarcted hearts, indicating decreased sensitivity to ischemia of the remodeled myocardium. Captopril treatment (3–8 weeks post myocardial infarction), which reversed hypertrophy without affecting the flow capacity of the coronary vascular bed, restored maximal cardiac perfusion. Ischemic ATP breakdown was not affected by captopril, whereas lactate release was even further reduced, suggesting alterations towards a more aerobic ATP production. These data indicate that despite the reduced maximal cardiac perfusion, the remodeled myocardium of infarcted hearts is less sensitive to ischemia. Reversal of hypertrophy by chronic captopril restored maximal cardiac perfusion and led to a better preservation of aerobic ATP production during ischemia.

Keywords: Myocardial infarction; Remodeling; Ischemia; Metabolism; Captopril

1. Introduction

Cardiac hypertrophy is regarded an independent risk factor for cardiovascular mortality (Levy et al., 1990). One of the proposed mechanisms is an increased sensitivity to ischemia of the hypertrophied myocardium. In rats, concentric but not eccentric hypertrophy is associated with enhanced ischemic vulnerability, which could be attributed to differences in cardiac perfusion (Harmsen et al., 1994). Myocardial infarction evokes compensatory hypertrophy of the non-infarcted myocardium of a mixed eccentric/concentric type, since myocyte dimensions increase both in width and in length (Anversa et al., 1985). The reactive hypertrophy after myocardial infarction is accompanied by interstitial (Van Krimpen et al., 1991a) and perivascular (Sun et al., 1994) fibrosis, and a reduction in capillary density (Anversa et al., 1985, 1986). These changes also occur in concentric hypertrophy, in which an increased sensitivity to ischemia has been reported (Canby and Tomanek, 1990). However, information about the ischemic vulnerability of the remodeled myocardium post myocardial infarction is not available yet.

Treatment with angiotensin converting enzyme inhibitors has now become a common therapy after myocardial infarction, since it improves the heart function and prognosis of patients (Pfeffer et al., 1992), as well as myocardial infarcted rats (Pfeffer et al., 1987; Schoemaker et al., 1991). An important mode of action of angiotensin converting enzyme inhibitor therapy is its effect on the structural changes in surviving myocardium post myocardial infarction. Captopril treatment prevents or reverses cardiac hypertrophy (Pfeffer et al., 1985) and interstitial fibrosis (Van Krimpen et al., 1991a) of the spared myocardium. However, it is still unknown whether these effects on remodeling also increase tolerance to ischemia. Promising results were obtained with enalapril treatment in spontaneously hypertensive rats (Schoemaker et al., 1994).

In the present study, sensitivity to ischemia in relation to cardiac hypertrophy and remodeling, as well as baseline

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and maximal cardiac perfusion, was investigated in rats with chronic myocardial infarction. In parallel, the effects of long-term captopril treatment were studied.

2. Materials and methods

Male, Wistar rats (270–320 g, Harlan, Zeist, Netherlands) were used in this study. Rats were housed under a 12-h light/dark cycle with standard rat chow and water available ad libitum. Captopril (Squibb, Princeton, NJ, USA) treatment (2 g/l of drinking water; Pfeffer et al., 1985, 1987) was started 3 weeks after infarction and was continued until the end of the experiment, 8 weeks after surgery. Since in previous studies no effects of long-term captopril treatment on hypertrophy or remodeling parameters in sham rats could be found (Van Krimpen et al., 1991b), we only studied effects of treatment on rats with myocardial infarction. The experiments were approved by the University Ethics Committee for the use of experimental animals.

2.1. Surgical preparation

Under pentobarbital (60 mg/kg i.p.) anesthesia, left anterior descending coronary artery ligation was performed as described in detail elsewhere (Fishbein et al., 1978; Pfeffer et al., 1979; Schoemaker et al., 1991). Briefly, after the trachea was intubated, an incision was made in the skin overlying the 4th intercostal space. The overlying muscles were separated and kept aside. The animals were put on positive pressure ventilation (frequency 65/min, tidal volume 3 ml), and the thoracic cavity was opened by cutting the intercostal muscles. The heart was left in situ and a 6-0 silk suture was looped under the left coronary artery near the origin of the pulmonary artery. The suture was tied except in sham operation. Ribs were pulled together with 3-0 silk. Subsequently, the muscles were returned to their normal position, and the skin was sutured.

2.2. Response to coronary vasodilators

Under pentobarbital anesthesia, the heart was rapidly excised and mounted for perfusion with an oxygenated Krebs-Henseleit buffer (composition in mM: NaCl 125, KCl 4.7, $CaCl_2$ 1.35, $NaHCO_3$ 20, NaH_2PO_4 0.4, $MgCl_2$ 1.0, D-glucose 10; pH = 7.4; 37°C) at a constant pressure of 85 mm Hg, using the Langendorff technique. Heart rate was kept constant at 350 beats/min by pacing with a Grass stimulator (Grass Medical Instruments, Quincy, MA, USA). A water-filled latex balloon was inserted into the left ventricle via the left atrium, and connected to a pressure transducer (Viggo-Spectramed, Oxnard, USA). The pressure signal was fed into a 68B09-based preprocessor and an AT compatible microcomputer for on-line recording of left ventricular pressure, its first derivative (dP/dt) and heart rate. Left ventricular end-diastolic pressure was set to 5 mm Hg by adjusting the balloon volume. Coronary flow was measured by an in-line flow-probe (Transonic Systems, Ithaca, NY, USA) placed in the tubing to monitor the flow of buffer passing through the probe just before the buffer entered the coronary arteries. After a stabilization period of 15 min, maximal coronary flow during vasodilation was determined. 0.1 ml of a 10^{-2} M adenosine solution (Janssen Chimica, Geel, Belgium) was injected into the perfusing buffer just before the buffer entered the coronary arteries, followed by a re-stabilization period, and subsequently 0.1 ml of a 10^{-2} M sodium nitroprusside solution (Department of Pharmacy, Academic Hospital Dijkzigt, Rotterdam, Netherlands) was injected into the perfusing buffer. These doses were found to induce a maximal effect, as determined from dose-response curves obtained in pilot experiments. Coronary flow is expressed as absolute values of ml/min, as an index for the flow capacity of the coronary vascular bed, as well as values corrected for heart weight (mainly myocytes), representing cardiac perfusion.

2.3. Ischemia and reperfusion

Perfusion pressure was abruptly lowered to 15 mm Hg. In pilot experiments, continued pacing during ischemia was often found to induce severe arrhythmia. Therefore, during ischemia, hearts were allowed to beat spontaneously. Because of the very low values, coronary flow during ischemia was measured by timed collection of coronary effluent. During the last minute of ischemia and the first minute of reperfusion, coronary effluent was sampled on ice and stored at −80°C until assayed for lactate and purines. After 30 min of low-flow ischemia, perfusion pressure was reset to 85 mm Hg. Maximal coronary flow during reperfusion (reactive vasodilation) was determined.

2.4. Determination of purines and lactate

The release of purines into the coronary effluent, calculated as concentration × flow per heart weight, was used to investigate loss of ATP catabolites from the myocytes (Schrader et al., 1977; Achterberg et al., 1984). The cardiac loss of ATP catabolites during ischemia correlates well with myocardial ATP breakdown, as measured with [^{31}P]nuclear magnetic resonance (Harmsen and Seymour, 1988). The concentration of purines was determined as described in detail by Smolenski et al. (1990). Briefly, the ATP catabolites uric acid, uracil, cytidine, adenosine, inosine, hypoxanthine, xanthine and uridine were determined by high-performance liquid chromatography on a C_{18}-μBondapak column (Millipore Waters Co., Milford, MA, USA). Coronary effluent (100 μl) was injected directly into the system, eluted with a 15% (v/v) solution of acetonitrile in 150 mM potassium dihydrogen orthophos-

phate, containing 150 mM potassium chloride adjusted to pH 6.0 with potassium hydroxide. Peaks were monitored by absorption at 254 nm.

The release of lactate into the coronary effluent was used as an indicator of the activity of anaerobic glycolysis in the cardiomyocyte (Vrobel et al., 1982). Lactate concentration in coronary effluent was determined as described in detail by Marbach and Weil (1967) (reagents, Sigma Diagnostics, Deisenhofen, Germany). Briefly, lactic acid was converted by lactate oxidase to pyruvate and H_2O_2. In the presence of the H_2O_2 formed, peroxidase catalyzed the oxidative condensation of chromogen precursors to produce a colored dye with an absorption maximum at 540 nm. Lactate concentration could be determined, being directly proportional to the increase of absorption at 540 nm.

2.5. Data analysis

Data are expressed as group means ± S.E.M., unless indicated otherwise. Only data from infarcted hearts with an infarct area comprising the major part of the left ventricular free wall were included in the study, since smaller infarctions are known to be hemodynamically fully compensated (Pfeffer et al., 1979; Schoemaker et al., 1991). Data were analyzed using one-way analysis of variance (ANOVA), followed by a post-hoc *t*-test (Wallenstein et al., 1980). Differences were considered statistically significant if $P < 0.05$.

3. Results

All infarctions were transmural and were located in the lateral (free) wall of the left ventricle. Four hearts, two in the untreated infarcted group and two in the captopril-treated infarcted group, were excluded from analysis because only a minor part of the left ventricular free wall was infarcted. Results comprise data from 7 sham hearts, 10 untreated infarcted hearts, and 7 captopril-treated infarcted hearts. Heart weight was significantly increased after myocardial infarction compared to that of sham-operated controls. Captopril treatment reduced the weight of infarcted hearts to sham values. Because body weight was also found to be decreased in captopril treated rats, the ratio of heart weight to body weight was not influenced by captopril treatment (Table 1).

3.1. Coronary vasodilation (Fig. 1)

Baseline coronary flow was lower in infarcted hearts, although this did not reach statistical significance. However, cardiac perfusion, coronary flow corrected for heart weight, was significantly depressed after myocardial infarction. Captopril treatment did not alter baseline coronary flow or cardiac perfusion.

Maximal *absolute* values for coronary flow, indicating the maximal flow capacity of the coronary vascular bed, were decreased in infarcted hearts with adenosine but not with nitroprusside. When corrected for heart weight, maximal cardiac perfusion with both vasodilators was reduced. Chronic captopril treatment restored maximal cardiac perfusion in infarcted hearts.

Table 1
Body weight and cardiac weight

	SHAM	MI	MI + CAP
BW (g)	417 ± 13	402 ± 10	341 ± 11 [a,b]
HWW (g)	1.08 ± 0.04	1.34 ± 0.07 [a]	1.07 ± 0.06 [b]
HWW/BW ($\times 10^{-3}$)	2.6 ± 0.1	3.3 ± 0.2 [a]	3.2 ± 0.2 [a]

MI, untreated infarcted hearts; MI + CAP, captopril-treated infarcted hearts; BW, body weight; HWW, heart wet weight; HWW/BW, heart wet weight to body weight ratio. [a] Significantly different from sham-operated rats; [b] significantly different from untreated infarcted rats.

Reactive vasodilation during reperfusion resulted in maximal values for cardiac perfusion similar to those obtained after administration of exogenous vasodilators for all groups (Table 2). Maximal reactive vasodilation was depressed in infarcted hearts, but was restored by captopril treatment.

3.2. Left ventricular function during ischemia and reperfusion (Fig. 2)

Under baseline conditions, left ventricular systolic pressure was significantly decreased after myocardial infarc-

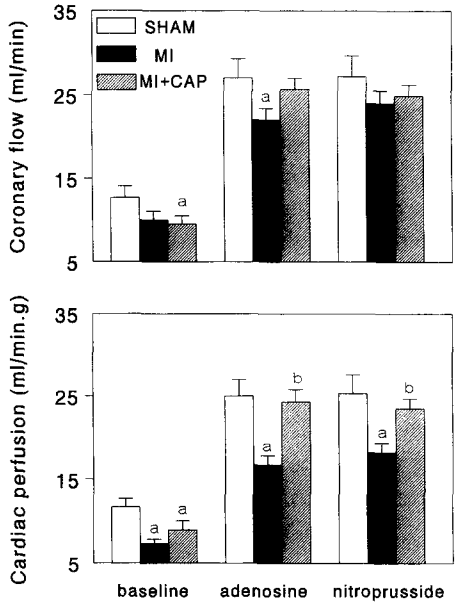

Fig. 1. Coronary flow (absolute values, upper panel) and coronary flow corrected for cardiac wet weight (cardiac perfusion, lower panel), at baseline and after intracoronary bolus injection of adenosine and nitroprusside. Open bars: sham hearts, black bars: untreated infarcted hearts (MI), hatched bars: captopril-treated infarcted hearts (MI + CAP). [a] Significantly different from sham values, [b] significantly different from untreated infarcted hearts.

Table 2
Peak cardiac perfusion after vasodilators and during reperfusion

	Maximal cardiac perfusion (ml/min·g)		
	SHAM	MI	MI+CAP
Adenosine	25.0±2.0	16.7±1.2 [a]	24.3±1.5 [b]
Nitroprusside	25.3±2.3	18.2±1.2 [a]	23.5±1.2 [b]
Reperfusion	23.5±1.2	15.2±1.1 [a]	20.8±1.0 [b]

Maximal cardiac perfusion (ml/min·g) after intracoronary injection of adenosine, of nitroprusside, and during reperfusion after 30 min of low-flow ischemia. MI, untreated infarcted hearts; MI+CAP, captopril-treated infarcted hearts. [a] Significantly different from sham hearts; [b] significantly different from untreated infarcted hearts.

tion (53 ± 7 vs. 79 ± 12 mm Hg in shams). Furthermore, contractility and relaxation were depressed in infarcted hearts, indicated by a decreased peak velocity of pressure change ($+(dP/dt)_{max}$ and $-(dP/dt)_{max}$). Chronic captopril treatment did not significantly alter these parameters (Fig. 2).

Lowering the perfusion pressure to 15 mm Hg resulted in low-flow ischemia (0.86 ± 0.05, 0.78 ± 0.07 and 0.78 ± 0.07 ml/min · g, in sham, untreated infarcted and captopril-treated infarcted hearts, respectively, at the beginning of the ischemic period). Resetting the perfusion pressure to 85 mm Hg induced reactive vasodilation with a maximum after approximately 1 min. Captopril restored the reduced maximal postischemic perfusion in infarcted hearts (Table 2), but did not influence perfusion at other time points.

Ischemia caused a marked bradycardia (heart rate 65 ± 19, 45 ± 5 and 53 ± 13 min^{-1} in sham, untreated infarcted and captopril-treated infarcted hearts, respectively, after 30 min of ischemia). Reperfusion quickly restored heart rate to baseline values (281 ± 29, 298 ± 17 and 277 ± 27 min^{-1} in sham, untreated infarcted and captopril-treated infarcted hearts, respectively, after 1 min of reperfusion). Furthermore, a profound depression of left ventricular function was present during ischemia. Pressure-rate product (left ventricular systolic pressure × heart rate), as an index of cardiac work, averaged 1710 ± 166 mm Hg · s^{-1} in sham hearts during ischemia and was significantly lower in infarcted hearts (953 ± 171 and 825 ± 218 mm Hg · s^{-1} in untreated and captopril-treated hearts, respectively). During reperfusion, parameters for left ventricular function were restored to baseline values. $+(dP/dt)_{max}$ was significantly lower in infarcted hearts compared to sham hearts during the entire experiment, while these differences for $-(dP/dt)_{max}$ and systolic pressure only reached statistical significance at baseline and during reperfusion. Captopril therapy did not significantly alter in vitro functional parameters in infarcted hearts at any timepoint.

3.3. Cardiac release of purines and lactate (Fig. 3)

During the last minute of ischemia, the concentration of purines in coronary effluent was significantly lower in infarcted hearts compared to sham hearts, and even further reduced after captopril treatment (Table 3). Since coronary flow was not similar for the experimental groups, purine *release* was calculated as concentration times flow per heart weight. Cardiac release of purines was lower in infarcted hearts than in sham hearts, but was not affected by captopril treatment. Similarly, during the first minute of reperfusion, release of purines was significantly lower in

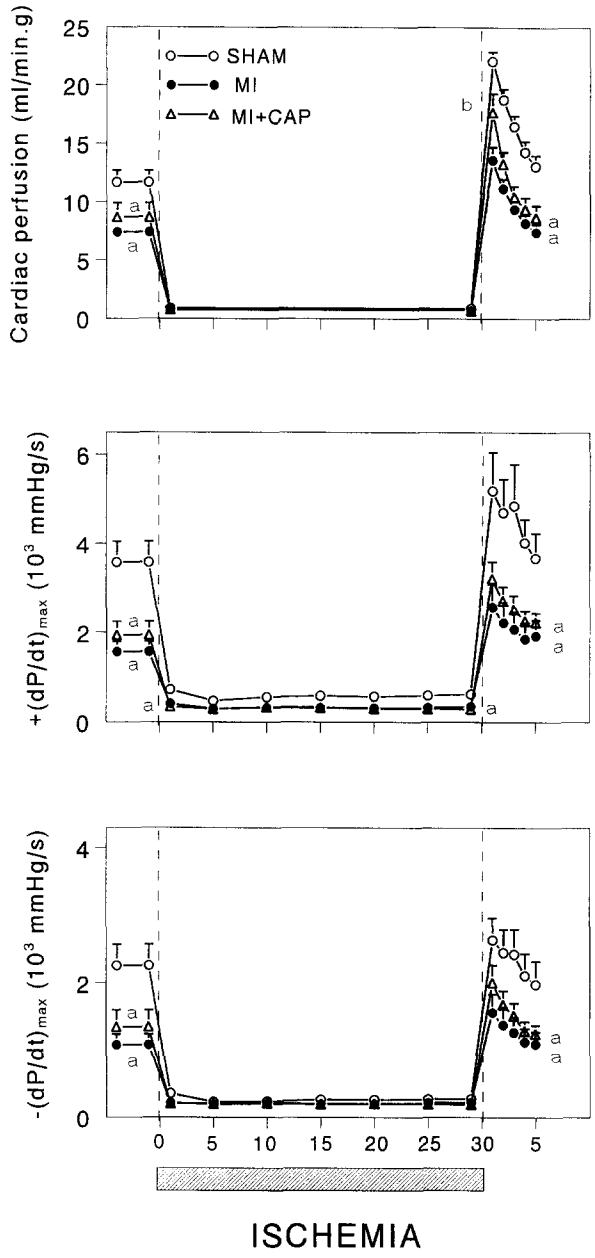

Fig. 2. Physiological parameters during Langendorff perfusion, at baseline, during ischemia and reperfusion. Open circles: sham hearts, black circles: untreated infarcted hearts (MI), triangles: captopril-treated infarcted hearts (MI+CAP). Upper panel: cardiac perfusion, middle panel: peak velocity of left ventricle pressure rise during contraction ($+(dP/dt)_{max}$), lower panel: peak velocity of left ventricle pressure decline during relaxation ($-(dP/dt)_{max}$). [a] Significantly different from sham values, [b] significantly different from untreated infarcted hearts.

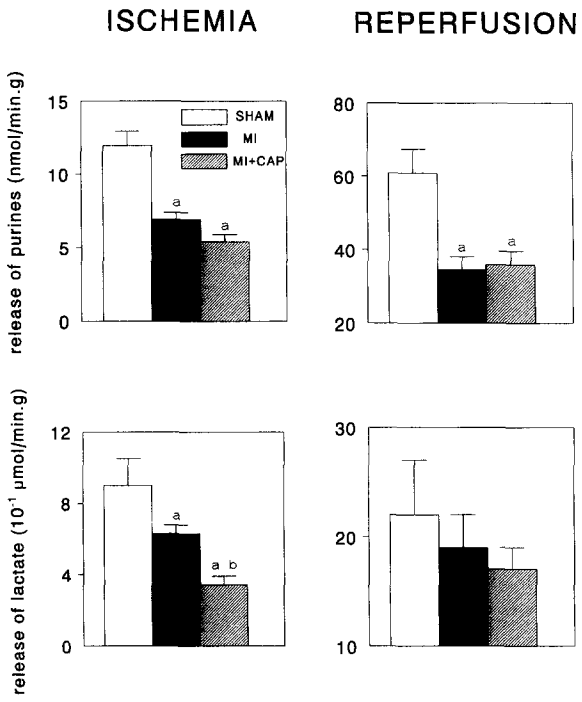

Fig. 3. Cardiac release of purines (upper 2 panels) and lactate (lower 2 panels) into coronary effluent, during ischemia (left panels) and reperfusion (right panels). Open bars: sham hearts, black bars: untreated infarcted hearts (MI), hatched bars: captopril-treated infarcted hearts (MI + CAP). [a] Significantly different from sham values, [b] significantly different from untreated infarcted hearts.

Table 3
Concentrations (μM) of purines and lactate in coronary effluent

		SHAM	MI	MI + CAP
Purines	Ischemia	13.1 ± 1.1	10.4 ± 1.1 [a]	7.3 ± 0.6 [a]
	Reperfusion	3.1 ± 0.3	3.1 ± 0.5	2.2 ± 0.2
Lactate	Ischemia	981 ± 134	941 ± 68	444 ± 56 [a,b]
	Reperfusion	111 ± 28	175 ± 42	103 ± 11

MI, untreated infarcted hearts; MI + CAP, captopril-treated infarcted hearts; Ischemia, last minute of 30 min of ischemia; Reperfusion, first minute of reperfusion. [a] Significantly different from sham hearts; [b] significantly different from untreated infarcted hearts.

untreated infarcted hearts compared to sham hearts, and not altered by captopril treatment (Fig. 3).

Lactate concentrations in coronary effluent were comparable in untreated infarcted hearts and sham hearts, but significantly reduced in captopril-treated infarcted hearts (Table 3). Cardiac release of lactate appeared to be significantly lower in infarcted hearts, and even further reduced after captopril treatment (Fig. 3).

4. Discussion

Hypertrophy and remodeling of the spared myocardium after myocardial infarction could increase the sensitivity to ischemia of this tissue, and hence the risk of additional morbidity, and mortality. In the present study, the sensitivity of remodeled, chronically infarcted hearts to acute ischemia in relation to cardiac perfusion, and the effects of long-term captopril treatment were studied.

4.1. Maximal vasodilation with adenosine and nitroprusside

Ischemia evokes release of vasodilatory substances like adenosine (Saito et al., 1981) and nitric oxide (Kostic and Schrader, 1992). Vascular changes associated with postinfarction remodeling, such as perivascular fibrosis (Sun et al., 1994), could mechanically restrict vasodilation. To investigate this possibility, maximal coronary flow in response to exogenous adenosine, as well as to nitroprusside, was measured.

Maximal coronary flow in response to adenosine, but not in response to nitroprusside, was found to be reduced in infarcted hearts. These *absolute* values, not corrected for heart weight, represent maximal flow through the coronary vascular bed. The observation that vasodilation induced by nitroprusside did not differ between infarcted hearts and sham hearts implies that the maximal flow capacity of the coronary vascular bed is not decreased in infarcted hearts. In the presence of a permanently occluded left descending coronary artery (one of the 3 major coronary arteries), a maximal flow that is not different from maximal flow in sham hearts indicates angiogenesis or growth of native vessels of the vascular bed of the remaining 2 patent coronary arteries. In the present study, only measurements of total coronary flow, without evaluation of regional distribution, were obtained. Therefore, the flow that is actually directed to the non-infarcted part of the left ventricle, which would have an increased metabolic demand to compensate for the loss of contractile tissue in the infarcted area, is unknown. Nevertheless, it is clear from our observations that the remodeling induced by myocardial infarction does not cause a mechanical limitation to vasodilation. This is in agreement with results from studies of experimental hypertension, showing that coronary medial thickening (not occurring in myocardial infarction hearts) rather than perivascular fibrosis is associated with decreased maximal vasodilation (Brilla et al., 1991). The reduced maximal flow with adenosine would then be related to changed pharmacological rather than to structural properties of the coronary vascular bed.

Maximal cardiac perfusion, coronary flow per heart weight, however, was decreased for both vasodilators. This is in agreement with results from in vivo studies of coronary reserve in the myocardial infarction rat model (Karam et al., 1990). The deficit in the increase of capillary surface relative to the increase of cardiomyocyte volume in postinfarction cardiac remodeling (Anversa et al., 1986) could be responsible for this phenomenon.

Captopril treatment did not affect baseline coronary flow nor cardiac perfusion, suggesting that direct vasodilat-

ing effects of captopril can be excluded. The observed effects may therefore be attributed to structural changes after long-term treatment rather than to direct effects of captopril. Captopril treatment in the present study reduced heart weight without affecting the maximal flow through the coronary vascular bed, and hence restored maximal cardiac perfusion. Similar findings have been reported with spontaneously hypertensive rats (Canby and Tomanek, 1989). The observation that regression of hypertrophy by captopril is associated with normalization of maximal cardiac perfusion, supports the hypothesis that a disproportionate growth of myocyte volume relative to cardiac vascularization is responsible for the reduced maximal cardiac perfusion in myocardial infarction hearts.

4.2. Vasodilation during reperfusion

The heart responds to transient ischemia with reactive vasodilation due to the release of vasodilatory substances, including nitric oxide (Kostic and Schrader, 1992) and adenosine (Saito et al., 1981). Maximal coronary flow during reperfusion, in the present study, reached values similar to those obtained with the vasodilators administered. These data indicate that maximal coronary vasodilation may indeed occur in vivo after an ischemic episode. Similar to the maximal values obtained after administration of vasodilators, peak cardiac perfusion during reperfusion was depressed in myocardial infarction compared to sham hearts and was restored after captopril treatment. The explanation for these findings may therefore be similar to that for the maximal vasodilation seen with the administered vasodilators.

4.3. Sensitivity to acute ischemia

Cardiac remodeling due to chronic hypertension can increase sensitivity to ischemia (Canby and Tomanek, 1990; Harmsen et al., 1994). The cardiac remodeling induced by pressure overload shows many similarities to post myocardial infarction remodeling, including myocyte hypertrophy, interstitial and perivascular fibrosis, and reduced capillary density. One of the explanations for enhanced ischemic vulnerability is the increased oxygen diffusion distance, caused by myocyte hypertrophy with a relatively inadequate increase in capillary surface area. This is supported by metabolic adaptions within the myocytes, including a shift from V_1 to V_3 isomyosin (Geenen et al., 1989), with a lower ATPase activity, and thus a lower oxygen consumption for the same force of contraction. In infarcted hearts, the marked depression of the peak velocity of the rise in left ventricular pressure, rather than the left ventricular pressure per se, indicates a more economical ATP usage.

Acute ischemia results in cardiomyocyte hypoxia, which in turn impairs oxidative phosphorylation (Wilson et al., 1977), the primary means of ATP production under normal conditions (high ATP yield). During ischemia, decreased ATP regeneration can finally result in the loss of ATP catabolites, purines, from the cell (Schrader et al., 1977). In order to preserve intracellular ATP levels during ischemia, anaerobic glycolysis is activated. However, anaerobic ATP production (low ATP yield) is insufficient to meet the cellular ATP demand (Hearse, 1979). Moreover, during anaerobic glycolysis intracellular pH falls, which hampers cell function (Katz, 1973).

In the present experiments, the ischemic release of ATP catabolites from myocardial infarction hearts was lower than from sham hearts, which cannot be explained by differences in coronary flow or heart weight. The decreased loss of ATP catabolites was also not attributable to a greater ATP production by anaerobic glycolysis in myocardial infarction hearts compared to sham hearts, since lactate release from infarcted hearts was lower as well. Therefore, the explanation for this phenomenon may rather lie in the lower ATP consumption in infarcted hearts, which would be in concordance with the slower contraction in the present study and with the isomyosin shift reported by Geenen et al. (1989). Despite the major differences in perfusion and ischemic release of ATP catabolites and lactate, functional recovery during reperfusion was almost complete in all groups, indicating no irreversible damage to the heart.

Although captopril treatment started after 3 weeks in infarcted rats has been found to restore in vivo heart function (Schoemaker et al., 1991) already after 2 weeks of treatment, an effect seen up to 3 months of treatment (Pfeffer et al., 1985), in vitro left ventricular function was not significantly improved. The discrepancy can probably be explained by the measurement of in vitro left ventricular function as mechanical parameter of isovolumic contraction at a fixed preload and heart rate, which may not correlate well with the in vivo pump capacity of the heart. Captopril treatment did not alter the reduction in ATP breakdown in infarcted hearts compared to sham hearts, but further reduced lactate release. Although angiotensin converting enzyme inhibitor treatment has been found to reverse the V_1 to V_3 isomyosin shift in infarcted hearts (Michel et al., 1988), in vitro cardiac dynamics were not changed accordingly by captopril. Thus, like untreated infarcted hearts, captopril-treated infarcted hearts probably have a lower ATP turnover than sham hearts. Moreover, since lactate release in infarcted hearts was even further reduced by captopril, aerobic ATP production during acute ischemia in infarcted hearts may be preserved longer after captopril treatment. It is feasible that the captopril-induced reversal of hypertrophy could contribute to a more aerobic metabolism during ischemia. By reversing hypertrophy but not vessel growth, captopril therapy would reduce the oxygen diffusion distance. This is supported by the restoration of maximal cardiac perfusion by captopril treatment. In hypertrophied rat hearts, due to pressure overload, chronic captopril therapy restored the capillary density

(Canby and Tomanek, 1989) and decreased myocyte sensitivity to hypoxia (Canby and Tomanek, 1990).

In conclusion, myocardial infarction-related cardiac remodeling was associated with a decreased maximal cardiac perfusion to administered as well as to endogenous vasodilators. However, infarcted hearts were less sensitive to an additional acute ischemic period, as indicated by a lower cardiac ATP breakdown. Captopril treatment resulted in a restoration of maximal cardiac perfusion. The decreased ischemic ATP breakdown in infarcted hearts was unaffected by captopril treatment, but was accompanied by a lower lactate release, suggesting an alteration towards a more aerobic ATP production.

4.4. Clinical implications

Since myocardial infarction commonly occurs as a complication of diffuse coronary artery disease, myocardial infarction patients will be at risk for additional ischemic attacks in the remaining myocardium. The reduced coronary reserve of cardiac perfusion in infarcted hearts, as indicated by reduced maximal cardiac perfusion, may limit cardiac function and lead to ischemia during periods of increased coronary flow demand, like during stress and exercise. Restoration of maximal perfusion with captopril may therefore reduce the number of ischemic episodes in myocardial infarction patients, and this would be, in addition to the hemodynamic improvement, another mechanism for increased exercise tolerance and improved clinical outcome.

Lactate production causes proton accumulation within the myocyte, which hampers cellular function in an already stressed hemodynamic situation. A reduced ischemic lactate production in captopril-treated myocardial infarction patients may save myocytes from acidosis-induced damage (Armiger et al., 1977).

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