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Determinants of coronary reserve in rats subjected to coronary artery ligation or aortic banding

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Abstract

Objective: We investigated whether decreased coronary reserve in hearts after coronary artery ligation or in hearts from rats after aortic banding can be related to remodeling of resistance arteries. **Methods:** Maximal coronary flow (absolute flow) and cardiac perfusion (flow corrected for heart weight) were determined in isolated, perfused rat hearts after adenosine or nitroprusside, at 3 and 8 weeks after coronary artery ligation or 4–5 weeks after aortic banding. Perivascular collagen and medial thickness of resistance arteries were determined by morphometry. **Results:** Maximal coronary flow of infarcted hearts had been restored to sham values at 3 weeks. Growth of cardiac muscle mass from 3 to 8 weeks exceeded the increase in maximal coronary flow, leading to a decreased perfusion at 8 weeks. A slight, transient increase in perivascular collagen, but no medial hypertrophy, was found after infarction. After aortic banding, perivascular fibrosis and medial hypertrophy led to a decreased maximal coronary flow in both the hypertrophied left and the non-hypertrophied right ventricle. Consequently, perfusion of the left ventricle was most severely reduced. **Conclusions:** Reduced maximal perfusion after aortic banding is determined by both cardiac hypertrophy and vascular remodeling. In contrast, during infarction-induced remodeling, reduction of perfusion is not determined by vascular remodeling, but mainly by disproportional cardiac hypertrophy relative to vascular growth.

Keywords: Coronary artery tone; Coronary reserve; Myocardial infarction; Hypertension; Hypertrophy; Resistance arteries; Vasodilation; Rat, heart

1. Introduction

A decreased coronary vasodilator reserve has been described in different animal models of pressure-overload-induced cardiac hypertrophy [1–6], and it is recognized to play a role in the transition from left ventricular hypertrophy to heart failure [7]. The flow capacity of the coronary vascular bed (absolute flow) is thought to depend on the total cross-sectional area (CSA) of the resistance vasculature, which can be changed by: (1) arteriolar growth during remodeling, increasing CSA [5], (2) medial layer hypertrophy of resistance arteries, decreasing CSA [3,6], or (3) loss of functional arterioles, arteriolar rarefaction, decreasing CSA [8]. The resultant change in flow capacity relative to the increase in cardiac mass determines cardiac perfusion (flow per gram of muscle mass).

In contrast to pressure-overload-induced hypertrophy, data concerning coronary reserve in reactive hypertrophy following myocardial infarction (MI) are relatively scarce [9–11]. Moreover, it is still unclear if remodeling of resistance arteries, including accumulation of collagen in the adventitia of resistance arteries [12], contributes to a decreased maximal cardiac perfusion.

The present study was carried out to investigate whether post-MI remodeling can be associated with a decreased coronary reserve, and, if coronary reserve would be impaired, whether this can be related to vascular remodeling of resistance arteries and/or to the stage of cardiac remodeling. Studies were performed using the rat MI model, at 3

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weeks, shortly after completion of scar formation [13] at the compensated stage of cardiac remodeling, and at 8 weeks when progression into decompensation occurs [14,15]. For comparison, hearts from rats with experimental renovascular hypertension were studied (interrenal aortic banding, IRAB). In this model, cardiac hypertrophy was expected in the left but not the right ventricle, whereas pronounced vascular pathology was anticipated in both left and right ventricle [3].

2. Methods

Male Wistar rats (270–320 g, Harlan Zeist, The Netherlands) were used in this study. Rats were housed with a 12 h light/dark cycle, standard rat chow and water available ad libitum. The experiments were carried out after approval of the University ethics committee for the use of experimental animals.

2.1. Myocardial infarction

Under pentobarbital (60 mg/kg, i.p.) anaesthesia, left anterior descending coronary artery ligation was performed as described in detail elsewhere [13,16,17]. Briefly, after the trachea was intubated, an incision was made in the skin overlying the 4th intercostal space, with the overlying muscles 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 (thoracotomy-sham group). Ribs were pulled together with 3-0 silk. Subsequently, the muscles were returned to their normal position, and the skin was sutured. Vascular remodeling and coronary reserve were studied at 3 and 8 weeks after surgery. Only data from infarcted hearts with an infarcted area comprising more than half of the left ventricular free wall surface were included in this study, since smaller infarctions are known to be haemodynamically fully compensated [16,17]. Infarct size was judged immediately after isolation of the heart, before functional data were obtained. In a previous study by our group, estimation of infarct size by macroscopic appearance proved to be a reliable method for exclusion of small infarctions. Planimetric measurement of infarct size afterwards showed that excluded infarctions indeed comprised $< 20\%$ of left ventricular circumference. Included MI hearts showed little variation in infarct size ($37 \pm 1\%$ of left ventricular circumference) [18].

2.2. Renovascular hypertension following interrenal aortic banding (IRAB)

Under pentobarbital (60 mg/kg, i.p.) anaesthesia, a midline laparotomy was performed. The intestines were kept aside with gauzes, and the abdominal aorta was exposed. In the segment between the left and right renal artery, a 23-gauge needle was positioned alongside the aorta. To make a fixed stenosis, the aorta was tied off together with the needle, except in sham operation (laparotomy-sham group). The needle was then removed, and the abdomen was sutured. Before isolation of the heart, at 4–5 weeks after surgery, polyethylene catheters were inserted into the carotid (PE-50) and femoral (PE-10) artery under pentobarbital anaesthesia, and connected to a pressure transducer (Viggo-Spectramed, Oxnard, USA), in order to measure the pressure gradient over the banded aortic segment. To evaluate unilateral renal atrophy due to chronic ischaemia, the ratio of left to right kidney weight was determined. Only animals with a left to right kidney weight ratio of < 0.9, indicative of left kidney atrophy, were included in the analysis.

2.3. Coronary vasodilation and distribution of coronary flow

Under pentobarbital anaesthesia, 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, D-glucose 10; pH = 7.4; 37°C) at a constant pressure of 85 mmHg, 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). Left ventricular end-diastolic pressure was set at 5 mmHg by adjusting the balloon volume. Coronary flow was measured by a flow-probe (Transonic Systems, Ithaca, NY, USA) placed in the tubing just before the aorta to monitor the flow of buffer passing through the probe just before entering the coronary arteries. After a stabilization period of at least 15 min, baseline values were obtained and maximal coronary flow during vasodilation was determined. Adenosine (0.1 ml of a 10^{-2} M solution, Janssen Chimica, Geel, Belgium) was injected into the perfusing buffer just before it entered the coronary arteries, as a fixed dose since baseline coronary flows were comparable for all groups, and maximal coronary flow was measured. After a re-stabilization period, similarly 0.1 ml of a 10^{-2} M nitroprusside solution (pharmacy of University Hospital Dijkzigt) was administered into the perfusing buffer. These doses of vasodilators were found to induce maximal effect in complete dose–response curves obtained in pilot experiments. Ventricles were weighed after removal of atria and large vessels.

In order to investigate the contribution of cardiac hypertrophy, in a separate group of rats subjected to IRAB as described above, regional distribution of coronary flow

was determined. The distribution of blood flow was determined with 15 ± 1 (s.d.) μm diameter microspheres labelled with either ^{113}Sn or ^{46}Sc (N.E.N. Dupont, Boston, USA). For each measurement (baseline and nitroprusside-induced maximal vasodilation), a suspension of about 8000 microspheres, labelled with one of the isotopes, was injected into the perfusing buffer just before it entered the coronary arteries. In pilot experiments, coronary flow after injection of about 25,000 microspheres (10.5 ± 2.4 ml/min, $n = 5$), did not differ from baseline coronary flow (11.4 ± 2.7 ml/min). Radioactivity was counted for 5 min in a γ-scintillation counter (Packard, Minaxi autogamma 5000), using a suitable window for discriminating the different isotopes. All data were processed by a set of specially designed computer programs [19].

2.4. Measurement of perivascular collagen

The amount of perivascular collagen was measured in 6 hearts randomly selected from each experimental group, using the method as described previously [18,20,21]. Briefly, the hearts were fixated by perfusion with 3.6% phosphate-buffered formaldehyde. The ventricles were cut into 4 slices from apex to base, after removal of the atria and the large vessels. The slices were kept in formaldehyde for at least 24 h. After fixation, the slices were dehydrated and paraffin-embedded. Deparaffinized 5 μm-thick sections were incubated for 5 min with 0.2% (wt/vol) aqueous phosphomolybdic acid, and subsequently incubated for 45 min with 0.1% Sirius Red F3BA (C.I. 35780, Polysciences Inc., Northhampton, UK) in saturated aqueous picric acid, washed for 2 min with 0.01 M HCl, dehydrated, and mounted with Entellan (Merck, Darmstadt, Germany). In each heart, perivascular collagen around 3–5 different resistance arteries (luminal diameter < 150 μm) in the right ventricle as well as 6–10 resistance arteries in the interventricular septum was measured. In infarcted hearts, arteries selected for measurement were located in vital myocardium and did not approximate the border zone of the infarction. The perivascular picrosirius-red-positive area was corrected for luminal area of the vessel [20].

2.5. Measurement of medial thickness

Deparaffinized sections were incubated for 90 min with a resorcin–fuchsin solution at 60°C, and subsequently for 2 min with a Van Giesson solution, flushed with alcohol, dehydrated, and mounted with Entellan (Merck, Darmstadt, Germany). The tunica media areas of 8–10 resistance arteries (luminal diameter < 150 μm) in interventricular septum and right ventricle were measured and corrected for luminal area. In infarcted hearts, arteries selected for measurement were located in vital myocardium and did not approximate the border zone of the infarction.

2.6. Data analysis

Results comprise data from 6 to 12 animals per group. Data are expressed as group means ± s.e.m., unless indicated otherwise. Effects of MI-induced remodeling were evaluated by comparing data from MI hearts with data from contemporary thoracotomy-sham hearts. Effects of hypertension-induced remodeling were evaluated by comparing data from IRAB hearts with data from laparotomy-sham hearts. Effects of time in MI-induced remodeling were assessed by comparison of deviation from sham values at 3 weeks and at 8 weeks after surgery. Finally, differences between effects of MI-induced and hypertension-induced remodeling were studied comparing deviation from sham values caused by coronary artery ligation and IRAB, respectively. Differences were tested for statistical significance using Student's t-test for independent groups, and were considered statistically significant if $P < 0.05$.

3. Results

3.1. Evaluation of MI and IRAB models

Coronary artery-ligated hearts showed large transmural infarctions, which were located in the lateral (free) wall of the left ventricle. A total of 6 out of 30 MI hearts (3 weeks and 8 weeks combined) were excluded from analysis

Table 1
Characterization of experimental groups

	Sham	MI 3 wk	Sham	MI 8 wk	Sham	IRAB
n	10	10	7	9	12	9
BW (g)	388 ± 11	371 ± 7	417 ± 13	401 ± 11	394 ± 11	363 ± 18
HWW (mg)	985 ± 37	928 ± 22	1080 ± 41	1336 ± 78 *	1066 ± 50	1261 ± 71 *
HWW/BW (×10^{-3})	2.6 ± 0.1	2.5 ± 0.1	2.6 ± 0.1	3.3 ± 0.2 *	2.7 ± 0.1	3.5 ± 0.1 *
L/R kidney weight					0.99 ± 0.02	0.45 ± 0.11 *

MI 3 wk = hearts 3 weeks after myocardial infarction; MI 8 wk = hearts 8 weeks after myocardial infarction; IRAB = hearts from interrenal aortic banded rats at 4–5 weeks after surgery; BW = body weight at end of protocol; HWW = heart wet weight; HWW/BW = heart wet weight to body weight ratio; L/R kidney weight = left to right kidney weight ratio.
* $P < 0.05$ versus sham values.

because the infarcted area comprised only a minor part of the left ventricular free wall. Despite the replacement of a considerable part of the myocardium by lighter scar tissue, wet weight of the entire heart was not decreased in MI hearts at 3 weeks. At 8 weeks after infarction, cardiac mass was even higher in MI hearts, indicative of progressive hypertrophy of surviving myocardium. This was reflected in a significantly increased heart wet weight to body weight ratio in MI hearts at 8 weeks (Table 1).

In rats after IRAB, both carotid and femoral artery blood pressure were measured to evaluate the pressure gradient over the banded aortic segment. Hypertension after IRAB was demonstrated by a significantly raised mean arterial blood pressure, as measured in the carotid

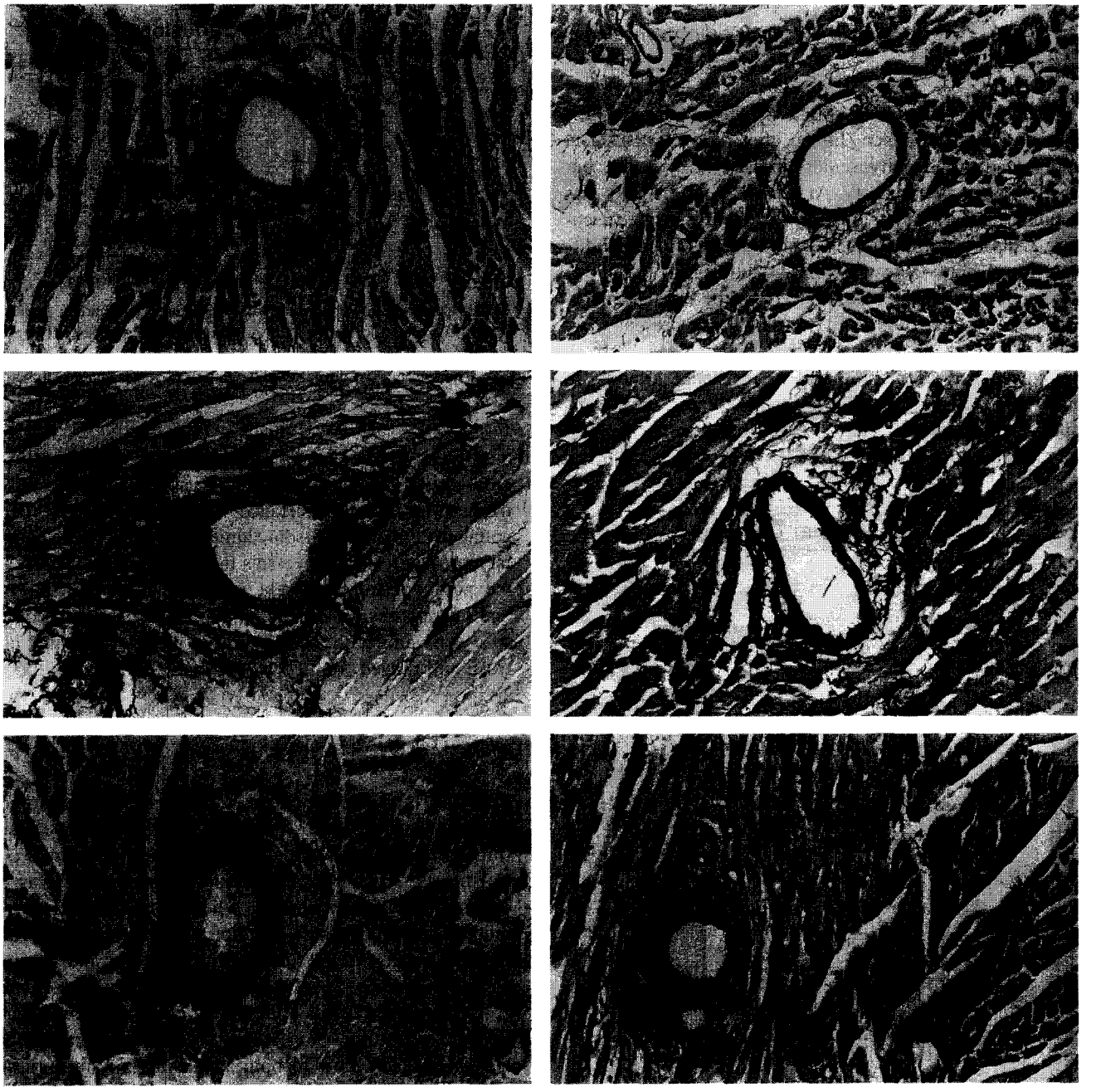

Fig. 1. Photomicrographs of picrosirius-red-stained sections (A,C,E) and resorcin–fuchsin-stained sections (B,D,F) showing resistance arteries: (A,B) normal myocardium after sham operation; (C,D) non-infarcted myocardium 3 weeks after MI (increased perivascular collagen, normal medial thickness); (E,F) heart from aortic banded rat (increased perivascular collagen, increased medial thickness). In photomicrograph F, the stained line within the tunica media (arrowhead) suggests growth of the tunica media outside its normal boundaries. The bar in photomicrograph A indicates 100 μm, and accounts for all photomicrographs.

artery (140 ± 8 versus 115 ± 4 mmHg). With a decreased blood pressure distal to the banded segment (95 ± 6 versus 115 ± 5 mmHg), a substantial pressure gradient was present after IRAB. After exclusion of 4 out of 13 banded rats, because of absence of unilateral kidney atrophy (left to right kidney weight ratio of < 0.9), IRAB significantly decreased left to right kidney weight ratio at 4 weeks. Cardiac hypertrophy was indicated by a significantly increased heart wet weight and heart wet weight to body weight ratio (Table 1).

3.2. Vascular remodeling in MI hearts and hearts after IRAB (Figs. 1 and 2)

MI-induced remodeling was associated with a significantly increased collagen/lumen area ratio of resistance arteries (indicating perivascular fibrosis) at 3 weeks, but not at 8 weeks after surgery. At neither 3 nor 8 weeks was the tunica media/lumen area ratio of the resistance vasculature within non-infarcted myocardium in MI hearts different from sham values (Fig. 1C,D and Fig. 2).

After IRAB, a striking change from the normal microscopic appearance of the myocardium was present (Fig. 1E,F). There were areas of focal necrosis as well as pronounced perivascular fibrosis of resistance arteries, in both the non-hypertrophied right ventricle and the hypertrophied left ventricle. The observed perivascular fibrosis was reflected in a distinct increase in the collagen/lumen area ratio. Media/lumen area ratio was significantly increased, indicating growth of the vascular smooth muscle medial layer of resistance arteries (Fig. 2). Both collagen/lumen and media/lumen area ratios were equally increased in resistance vessels in the hypertrophied left and the non-hypertrophied right ventricle. Both in MI hearts and hearts after IRAB, lumen diameters of measured vessels were similar to those analyzed in sham-operated controls, and ranged from 35 to 140 μm.

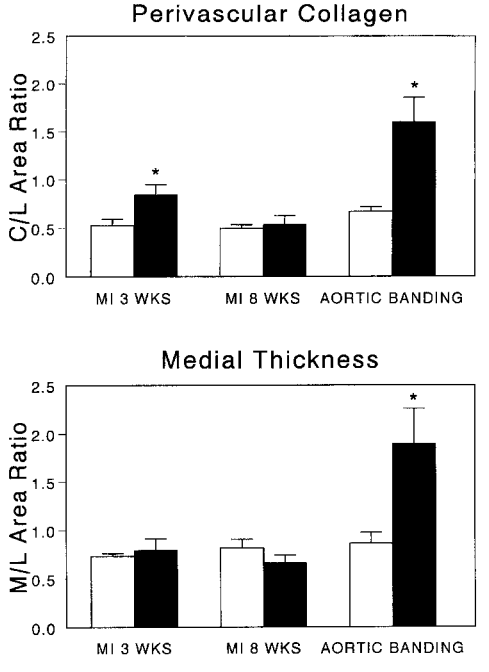

Fig. 2. Remodeling of resistance arteries in non-infarcted myocardium of MI hearts at 3 and 8 weeks, or hearts from rats after aortic banding (black bars) and hearts from sham-operated rats (white bars). Upper panel: perivascular collagen as measured by collagen to lumen (C/L) area ratio. Lower panel: tunica media thickness as measured by medial to lumen (M/L) area ratio. * $P < 0.05$ versus sham values.

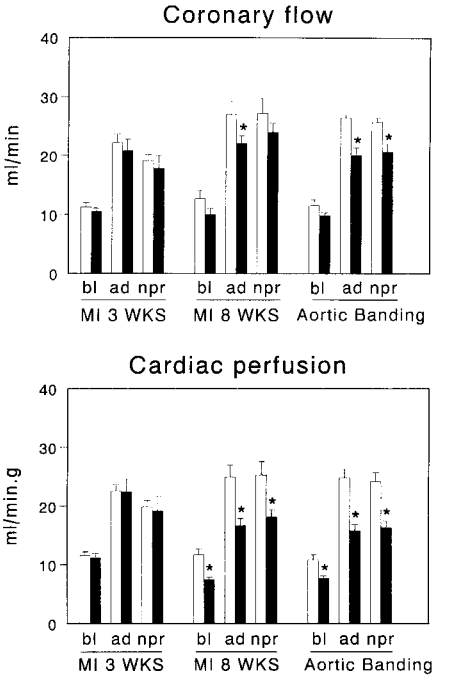

Fig. 3. Coronary flow (absolute values, ml/min) and cardiac perfusion (values corrected for heart weight, ml/min · g) in hearts after MI or aortic banding (black bars) and sham operation (white bars). bl = baseline; ad = adenosine; npr = nitroprusside. * $P < 0.05$ versus sham values.

3.3. Coronary flow and tissue perfusion of remodeled hearts (Fig. 3)

In hearts at 3 weeks after MI, both baseline and maximal coronary flow (ml/min), as well as tissue perfusion (ml/min · g) were not decreased compared to normal control hearts. At 8 weeks, baseline coronary flow was not different from sham values, whereas maximal flow was reduced with adenosine but not with nitroprusside. Corrected for mass of perfused tissue, baseline and maximal perfusion (with either of the 2 vasodilators) was decreased.

In remodeled hearts after IRAB, coronary flow at baseline did not differ from values in sham-operated control hearts, but peak flow to both adenosine and nitroprusside was reduced. Myocardial perfusion was decreased both at baseline and during maximal vasodilation, compared to control hearts.

Ratios of maximal/baseline coronary flow (or maximal/baseline perfusion) did not differ between remodeled

Table 2
Ratio of maximal to baseline coronary flow

	Sham	MI 3 wk	Sham	MI 8 wk	Sham	IRAB
Adenosine	2.0±0.1	2.0±0.2	2.3±0.4	2.4±0.2	2.5±0.2	2.1±0.1
Nitroprusside	1.7±0.1	1.7±0.2	2.4±0.5	2.6±0.2	2.4±0.2	2.1±0.2

Ratios of maximal coronary flow after intracoronary injection of vasodilators and baseline coronary flow. MI 3 wk = hearts 3 weeks after myocardial infarction; MI 8 wk = hearts 8 weeks after myocardial infarction; IRAB = hearts from interrenal aortic banded rats.

hearts and sham-operated control hearts, although it tended to be lower in hearts after IRAB (Table 2).

3.4. Distribution of coronary flow after IRAB (Fig. 4)

In IRAB rats used to study regional distribution of coronary flow, there was only a modest increase in heart wet weight (987 ± 51 vs. 922 ± 60 mg, n.s.). This was totally attributable to the left ventricle, since right ventricular weight did not differ from sham values (163 ± 4 vs. 188 ± 12 mg, n.s.). Left ventricular hypertrophy was indicated by a significantly increased left ventricle/body weight ratio (2.7 ± 0.2 vs. 2.2 ± 0.1 mg/g). Baseline coronary flow and myocardial perfusion were not affected in these hearts, in either the right or the left ventricle. During nitroprusside-induced maximal vasodilation, coronary flow was restricted equally in left and right ventricles of banded rats (29 ± 7 vs. 33 ± 4% decrease versus sham values). However, corrected for tissue mass, left ventricular perfusion (hypertrophy present) was more affected than perfusion of the right ventricle (no hypertrophy) (37 ± 5 vs. 22 ± 5% decrease compared to sham values).

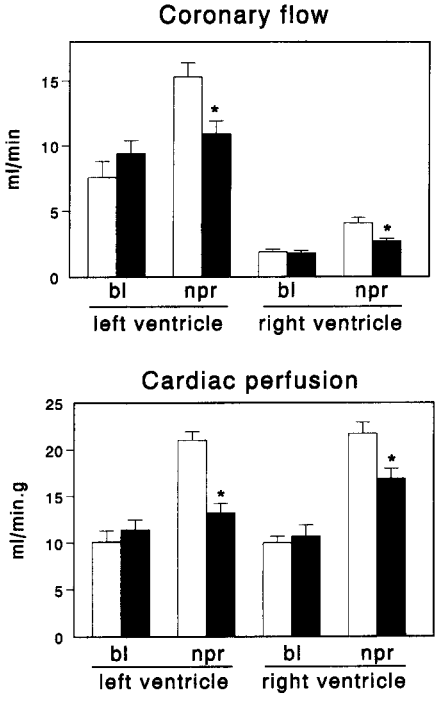

Fig. 4. Coronary flow (absolute values, ml/min) and cardiac perfusion (values corrected for heart weight, ml/min·g) in left and right ventricles of hearts 4–5 weeks after aortic banding (black bars) and sham operation (white bars). bl = baseline; npr = nitroprusside. $^{*}P < 0.05$ versus sham values.

4. Discussion

In pressure-overload-induced cardiac hypertrophy, a decreased coronary reserve has been recognized as a potential mechanism for the eventual development of heart failure [7]. Relative to the amount of information about coronary reserve in pressure-overload-induced hypertrophy [1–6], studies on flow reserve in MI-induced reactive hypertrophy are scarce. The aim of the present study was to measure flow capacity of the coronary vascular bed as well as tissue perfusion, and to identify determinants of a decreased coronary reserve in MI hearts. The main findings were: (1) flow capacity of the coronary vascular bed in MI hearts had been restored to sham values at 3 weeks; (2) progression of post MI cardiac hypertrophy from 3 to 8 weeks exceeded the increase in flow capacity, causing a decreased myocardial perfusion at 8 weeks; and (3) perivascular collagen accumulation in MI hearts appeared to be transient and comparatively mild in relation to the perivascular fibrosis seen in hearts after renovascular hypertension, and was not related to the decreased coronary reserve.

4.1. Flow capacity of the coronary vascular bed in MI hearts

In the rat MI model, permanent occlusion of one of the 3 coronary arteries will acutely lead to a substantial reduction of the coronary vascular bed. Maximal coronary flow is assumed to be determined by total cross-sectional area (CSA) of the resistance vasculature. The restored flow capacity at 3 weeks after coronary artery ligation, despite the initially considerably reduced total CSA, implies angiogenesis in the vascular beds perfused by the two remaining coronary arteries. Post-MI angiogenesis involves growth of capillaries [22], but would also include arteriolar growth, as observed in pressure-overload-induced hypertrophy [5]. An increase in size and/or number of arterioles would increase the total CSA of the resistance vasculature perfused by the remaining 2 patent coronary arteries.

4.2. Progression of hypertrophy versus increase of flow capacity in MI hearts

Maximal flow capacity was 15% higher at 8 weeks compared to 3 weeks after MI, indicating an equivalent increase in CSA. However, this was exceeded by the increase in myocyte mass; MI hearts weighed 44% more at 8 weeks compared to 3 weeks. Therefore, the decreased baseline and maximal cardiac perfusion at 8 weeks can be explained by an inadequate growth of the vasculature relative to the growth of cardiac muscle. Our observation of an impaired maximal cardiac perfusion, associated with a disproportional growth of muscle mass relative to growth of the vasculature, is in agreement with data of Karam and co-workers [9] who found a 43% decrease of maximal tissue perfusion in left ventricles, and a 33% decrease in right ventricles of MI hearts, while myocyte size was significantly increased in both left and right ventricles.

Similar to our findings, Nelissen-Vrancken et al. [11] found a time-related normalization of maximal coronary flow, but a disproportional increase in tissue mass compared to maximal coronary flow. However, the latter was found in right ventricles and interventricular septa of MI hearts, but not in the region where the most pronounced hypertrophy would be expected (surviving part of the left ventricular free wall) [23]. This may be explained by the fact that effects of time in MI-induced remodeling were evaluated by comparing the timepoints of 1 week and 3 weeks after MI, although a substantial increase in regional tissue mass may occur in the first week after MI [24].

4.3. Comparison of maximal flow and perfusion of isolated hearts with in vivo data

Comparing our in vitro data with in vivo measurements in the rat MI model [10] revealed that at 8 weeks coronary reserve determined with radioactive microspheres as the ratio of maximal to baseline flow was reduced. However, in vivo coronary flow at baseline was slightly higher in MI than in normal hearts and was based on measurements using only the non-infarcted myocardium. In recent experiments, buffer flow to infarcted tissue of MI hearts averaged about 8% of total coronary flow (data not shown). Thus, total baseline coronary flow of MI hearts in vivo may have been even higher. Therefore, a higher coronary flow at baseline, possibly due to the haemodynamic state, rather than a decreased flow capacity would be responsible for the reduced coronary reserve. Both baseline and maximal coronary flow of buffer-perfused hearts were higher than that of the blood-perfused hearts from the aforementioned studies [9,10], probably due the higher viscosity of blood than buffer. However, the ratios of maximal to baseline coronary flow of sham hearts were comparable. Moreover, we have shown that in vitro maximal coronary flow with either nitroprusside or adenosine is comparable to the values during post-ischaemic vasodilation [25], indicating that the decreased maximal tissue perfusion in vitro in fact represents an actual limitation of this parameter in vivo.

4.4. Vascular remodeling and coronary reserve in MI hearts

A decreased maximal coronary flow could be attributed to remodeling of resistance arteries [6]. Remodeling of resistance arteries in MI hearts appeared to be confined to accumulation of perivascular collagen. No tunica media hypertrophy was found in MI hearts. Furthermore, the collagen accumulation was transient and relatively mild compared to the perivascular fibrosis observed in hearts from IRAB animals. Moreover, the perivascular collagen accumulation in MI hearts at 3 weeks was not associated with a reduction in maximal coronary flow capacity or myocardial perfusion, whereas the depressed maximal tissue perfusion at 8 weeks occurred without perivascular fibrosis. Therefore, the reduced maximal tissue perfusion in MI hearts could be attributed to a reduced density rather than to remodeling of resistance arteries.

4.5. Vascular remodeling and coronary reserve in hearts after pressure overload

In contrast to MI hearts, morphometry of resistance arteries in hearts from rats with renovascular hypertension revealed severe perivascular fibrosis and a prominent hypertrophy of the tunica media. Medial hypertrophy has been attributed to a hypertension-induced increase of perfusion pressure [6]. Thus, hypertension probably contributed to the development of the vascular pathology after aortic banding. Medial hypertrophy of resistance arteries may account for a decreased maximal CSA, although the perivascular collagen accumulation could have contributed to the reduced maximal flow capacity and perfusion as well. However, Brilla and co-workers [6] showed that in spontaneously hypertensive rats, the reduced coronary reserve was only normalized with regression of both perivascular fibrosis and the medial hypertrophy of resistance arteries (with high-dose lisinopril), and not by regression of perivascular fibrosis alone (with low-dose lisinopril). In the present study, vascular remodeling of resistance vessels was comparable in the hypertrophied left ventricle and in the non-hypertrophied right ventricle, resulting in an equal reduction of maximal coronary flow. Consequently, peak myocardial perfusion of the left ventricle was more affected than right ventricular perfusion. Apparently, vascular remodeling in renovascular hypertension controls maximal flow capacity, while hypertrophy of the surrounding myocardium determines the severity of maximal perfusion reduction.

5. Conclusion

Prominent vascular remodeling after aortic banding, including severe perivascular fibrosis and tunica media hypertrophy of resistance arteries, limits the flow capacity of the coronary vascular bed. Thus, in hypertension-induced hypertrophy, the reduction of maximal cardiac perfusion is determined by both vascular remodeling and the degree of cardiac hypertrophy. In MI-induced cardiac remodeling, a mild and transient perivascular fibrosis was observed, without medial hypertrophy. Coronary flow capacity had been restored, whereas maximal tissue perfusion was decreased at 8 weeks, when vascularization was lagging behind cardiac hypertrophy. In MI-induced cardiac remodeling, reduction of cardiac perfusion is not determined by vascular remodeling, but mainly by disproportional cardiac hypertrophy relative to vascular growth. Regression of cardiac hypertrophy or stimulation of vascular growth may therefore be appropriate pharmacotherapeutic strategies to restore the reduced coronary reserve after MI.

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