Minimal impairment of myocardial blood flow responses to exercise in the remodeled left ventricle early after myocardial infarction, despite significant hemodynamic and neurohumoral alterations

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Received 20 March 2001; accepted 20 July 2001

Abstract

Objectives: Previous studies have demonstrated a decreased flow reserve in the surviving hypertrophied left ventricle (LV) early after myocardial infarction. We hypothesized that exacerbation of hemodynamic abnormalities and neurohumoral activation during exercise could exhaust coronary flow reserve and thereby impair myocardial \( O_2 \) supply. Consequently, we studied hemodynamic, neurohumoral and regional myocardial perfusion and metabolic responses to exercise in pigs with LV hypertrophic remodeling 3 weeks after a myocardial infarction produced by permanent left circumflex coronary artery ligation.

Methods: Chronically instrumented pigs were exercised on a treadmill up to 85% of maximum heart rate. Pigs with a myocardial infarction (MI) had a lower cardiac output (21%), stroke volume (28%), LV \( dP/dt \) (18%), systemic (22%) and pulmonary (20%) vascular conductance, and increased left atrial (225%) and pulmonary artery (75%) pressures, compared to normal pigs. In MI, the exercise-induced increases in cardiac pump function, and systemic and pulmonary vasodilation were blunted compared to normals. Consequently, perfusion of visceral organs became impaired during strenuous exercise, but cerebral and skeletal muscle blood flows were maintained. Exercise-induced increases in norepinephrine and endothelin levels were exacerbated and, while relative sympathetic drive was maintained, cardiac responsiveness to norepinephrine was blunted. Despite lower capillary densities in the hypertrophied non-infarcted LV and relative subendocardial hypoperfusion during strenuous exercise, which necessitated a slight increase in \( O_2 \) extraction, there was no metabolic evidence of overt myocardial ischemia during strenuous exercise as indicated by the arterio-coronary venous \( pH \) difference. Conclusions: LV dysfunction and neurohumoral activation were present in pigs with a 3-week-old infarction, particularly during exercise. However, although myocardial perfusion and \( O_2 \) supply were slightly impaired, myocardial ischemia did not occur even during exercise up to 85% of maximum heart rate, suggesting that perfusion abnormalities do not contribute to LV dysfunction early after infarction. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Heart failure; Hemodynamics; Hypertrophy; Infarction; Oxygen consumption; Regional blood flow; Ventricular function

1. Introduction

Heart failure is currently the only major cardiovascular disorder of which the incidence is increasing. Myocardial infarction is becoming an increasingly important risk factor for heart failure due to the reduction in acute infarction-associated mortality. The role of myocardial blood flow (MBF) abnormalities in the progression of left ventricular (LV) dysfunction following infarction to overt heart failure is incompletely understood, but in vivo studies in rats [1,2] and pigs [3] indicate a reduction in MBF reserve of up to 35% in the surviving post-infarct LV myocardium, 3–8 weeks after infarction. Since hemodynamic and neurohumoral abnormalities associated with LV dysfunction are exacerbated during exercise, MBF increments could be impaired during increased \( O_2 \) demand produced by exer-
cise, thereby limiting myocardial $O_2$ availability. Consequently, we investigated the responses of MBF and myocardial metabolism to treadmill exercise in normal pigs (N) and pigs with a 3-week-old myocardial infarction (MI) to determine whether impaired MBF responses limit myocardial $O_2$ availability and result in myocardial ischemia. Since this is the first study of the responses to exercise in pigs with a myocardial infarction, we also determined the exercise-responses of LV function, systemic and pulmonary hemodynamics, and neurohormones.

2. Methods

2.1. Animals

Studies were performed in accordance with the Guide for the Care and Use of Laboratory Animals (NIH publication 86-23, revised 1985), and with approval of the Animal Care Committee of the Erasmus University Rotterdam. Thirty-three 2–3-month-old Yorkshire X Landrace pigs (23±1 kg at the time of surgery) of either sex entered the study; 17 were designated to the MI group and 16 to the N group. Daily adaptation of animals to laboratory conditions started 1 week before surgery.

2.2. Surgery

Pigs were sedated (ketamine, 20 mg/kg i.m.), anesthetized (thiopental, 10 mg/kg i.v.), intubated and ventilated with $O_2$ and $N_2O$ to which 0.2–1% (v/v) isoflurane was added [4–7]. Anesthesia was maintained with midazolam (2 mg/kg followed by 1 mg/kg per h i.v.) and fentanyl (10 $\mu$g/kg per h i.v.). Under sterile conditions, the chest was opened via the fourth left intercostal space and a fluid-filled polyvinylchloride catheter was inserted into the aortic arch for mean aortic pressure measurement (Combintrans® pressure transducers, Braun) and blood sampling for determination of blood gases (Acid-Base Laboratory Model 505, Radiometer), $O_2$ saturation and hemoglobin concentration (OSM2, Radiometer), and computation of $O_2$ content, $O_2$ supply, and $O_2$ consumption ($V_{O_2}$) [6,7]. An electromagnetic flow probe (14–15 mm, Skalar) was positioned around the ascending aorta for measurement of aortic blood flow. A microtipped pressure transducer ($P_{a\cdot s}$, Konigsberg Instruments) was inserted into the LV via the apex. Polyvinylchloride catheters were inserted into the pulmonary artery to measure pressure, administer drugs and collect mixed venous samples [6,7]. An angiocatheter was inserted into the anterior interventricular vein for blood sampling, while a Doppler flow probe (2.0–3.0 mm, Crystal Biotech) was placed around the left anterior descending coronary artery [6,7]. The proximal left circumflex coronary artery (LCx) was permanently occluded in 17 MI [4,8], which were monitored for 1 h and if needed internally defibrillated (10–30 J). Two MI died due to recurrent fibrillation. Catheters were tunneled to the back and animals were allowed to recover, receiving analgesia (0.3 mg buprenorphine i.m.) for 2 days and antibiotic prophylaxis (25 mg/kg amoxicillin and 5 mg/kg gentamycin i.v.) for 5 days [6,7]. Four MI died during the first night after surgery.

2.3. Experimental protocols

Central and regional systemic, pulmonary and coronary hemodynamic and neurohumoral responses to exercise were studied in 16 N (31±1 kg) and 11 MI (29±1 kg), at 19±2 and 20±1 days post-surgery, respectively. After baseline measurements (lying, $0_s$; and standing, $0_s$) were obtained, a five-stage treadmill exercise protocol was begun (1–5 km/h in N and 1–4 km/h in MI); data were collected during the last 30 s of each 3-min exercise stage [6,7].

2.3.1. Regional blood flows

In 11 N and 10 MI, regional blood flows were determined using the radioactive microsphere technique [5,9]. In N, radioactive microspheres were injected at rest (lying) and during exercise at 3 and 5 km/h. In MI, microspheres were injected at rest (lying) and during exercise at 3 and 4 km/h.

2.3.2. Time course

To study the progression of LV dysfunction over time, hemodynamic responses to treadmill exercise were additionally studied in nine N at 10±1 and 32±2 days, and in nine MI at 9±1 and 32±1 days after surgery.

2.4. Coronary morphometry

In six N and seven MI (arbitrarily chosen), hearts were fixed with 3% buffered formaldehyde via perfusion fixation and the anterior LV wall at mid-papillary level was dissected for morphometric analysis, dehydrated and embedded in paraffin. A minimum of four sections (4-μm thickness) were obtained, mounted on poly-l-lysine-coated glass slides, rehydrated and stained with hematoxylin–eosin (routine staining), resorcin–fuchsin to stain the elastic layers of arterioles, or lectin to stain capillary walls. Using a microscopy image analysis system (Impak C, Clemex Vision Image analysis system, Clemex Technologies) slides were analyzed at ×200 and ×400 magnification for arteriolar (40–120 μm) and capillary densities, respectively.

2.5. Data analysis

Digital recording and off-line analysis of hemodynamics and regional blood flows have been described previously.
[5–7]. Epicardial coronary artery Doppler blood flow measurements show an excellent correlation with myocardial tissue blood flow measurements with the radioactive microsphere technique [6,9]. Consequently, Doppler flow data were normalized per gram of myocardium using the flow data obtained with the radioactive microsphere technique [9]. In arterial blood samples, catecholamines, renin, angiotensin II, atrial natriuretic peptide (ANP), N-terminal ANP (N-ANP), and endothelin were determined, for references see [8]. Statistical analysis was performed using two-way (exercise level and infarction) analysis of variance (ANOVA) for repeated measures, followed by Dunnett's test (exercise effect) or unpaired t-testing (MI versus N). Analysis of co-variance (ANCOVA) for repeated measures was used to test for statistically significant differences in relations between hemodynamic or neurohumoral variables and body or myocardial \( \text{VO}_2 \) (with \( \text{VO}_2 \) as a co-variate) and between hemodynamic variables and norepinephrine (with norepinephrine as a co-variate) in MI versus N. Significance was accepted when \( P<0.05 \). Data are mean±S.E.M.  

3. Results  

3.1. Hemodynamics and \( \text{O}_2 \) transport and \( \text{O}_2 \) utilization  

3.1.1. Systemic hemodynamics  

Under resting conditions, MI were characterized by a lower cardiac output (21%), stroke volume (28%), and \( \text{LV} \frac{dP}{dt_{\text{max}}} \) (18%), compared to N, while left atrial pressure was approximately 2-fold higher (all \( P<0.05 \)) and heart rate tended to be higher (12%, \( P=0.07 \); Fig. 1). Mean aortic pressure was maintained in MI due to a 22% increase in heart rate and a 22% decrease in systemic vascular conductance. 

Fig. 1. Cardiovascular function in exercising MI ~3 weeks after myocardial infarction. \( 0_l= \) lying, \( 0_s= \) standing. Data are mean±S.E.M.; *\( P<0.05 \) versus \( 0_l, ^*P<0.05 \) MI versus Normal at corresponding exercise level.
decrease in systemic vascular conductance. In MI, the exercise-induced responses of cardiac output, LV dP/dt\(_{\text{max}}\), LV systolic pressure and systemic vascular conductance were blunted compared to N.

### 3.1.2. Pulmonary hemodynamics

In resting MI, mean pulmonary artery pressure was elevated (75%), due to a higher left atrial pressure and a lower pulmonary conductance (Fig. 1). In both MI and N, mean pulmonary artery pressure increased during exercise but, in contrast to N, pulmonary vascular conductance did not increase in MI.

#### 3.1.3. Systemic O\textsubscript{2} transport and O\textsubscript{2} utilisation

Arterial P\textsubscript{O\textsubscript{2}} was slightly lower in MI (98±3 mmHg at rest and 93±6 mmHg at 4 km/h) than in N (107±1 and 104±3 mmHg, respectively), but this did not result in arterial hemoglobin desaturation (Fig. 2). In MI, mixed venous SO\textsubscript{2} was lower than in N, both at rest and during exercise, reflecting an increased O\textsubscript{2} extraction which compensated for the lower cardiac output. Consequently, body Vo\textsubscript{o} index (i.e., body Vo\textsubscript{o} per kg body weight) was maintained in MI. There were no differences in arterial or mixed venous P\textsubscript{CO\textsubscript{2}} or pH between MI and N (not shown).

#### 3.1.4. Time course of hemodynamics and O\textsubscript{2} transport and O\textsubscript{2} utilisation

The hemodynamic responses to exercise between ~10 and ~32 days after surgery did not change in MI and N (Fig. 3). Stroke volume and BV\textsubscript{o} increased over this period, but this was likely due to body growth (from 25±1 to 33±1 kg in MI and from 26±1 to 33±1 kg in N), because stroke volume index (not shown) and BV\textsubscript{o} index were unchanged. These findings indicate that the degree of LV dysfunction and the circulatory adaptations in MI were stable over this time period.

### 3.2. Regional blood flows

In MI, resting blood flows and exercise-responses of blood flow to the brain, adrenals, spleen and various skeletal muscle groups were similar to those in N (Fig. 4), but the relations between body Vo\textsubscript{o} and blood flow to kidneys, small intestine, and pancreas were shifted towards lower blood flows (P<0.05 by ANCOVA).

#### 3.3. Neurohormones

In MI, circulating levels of renin, angiotensin II and aldosterone were not different from N under resting conditions, while norepinephrine, epinephrine and ANP tended (all P>0.10) to be higher. Endothelin levels (Fig. 5) and N-ANP levels (1.04±0.19 vs. 0.71±0.10 nmol/l, P<0.05, one-tailed), however, were significantly elevated in MI. Linear regression analysis of pooled individual data of both MI and N as well as of individual data within the MI group showed that in resting pigs endothelin levels correlated with pulmonary artery pressure (r\textsuperscript{2}=0.49 and r\textsuperscript{2}=0.75, respectively, both P<0.01) and correlated inversely with pulmonary vascular conductance (r\textsuperscript{2}=0.58 and r\textsuperscript{2}=0.66, respectively, both P<0.01).

In MI, exercise resulted in exaggerated increases in circulating levels of norepinephrine, epinephrine, and ANP (all P<0.05 versus rest, and P<0.05 versus N), while endothelin, angiotensin II and aldosterone increased in MI (all P<0.05 versus rest at 4 km/h) but not in N. However, the exercise-induced increases in aldosterone, angiotensin II and the trend towards increased renin (P=0.11) in MI were not different from the responses in N.

Fig. 6 illustrates that the norepinephrine response to exercise, plotted as a function of percent of estimated maximum BV\textsubscript{o}, was similar in MI and N, indicating a preserved relative sympathetic drive. In contrast, cardiac

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**Fig. 2.** Whole body O\textsubscript{2} balance in exercising MI ~3 weeks after myocardial infarction. Vo\textsubscript{o}, O\textsubscript{2} consumption. Data are mean±S.E.M.; *P<0.05 versus 0\textsubscript{L}, †P<0.05 MI versus Normal at corresponding exercise level.
Fig. 3. Time course of LV pump function and whole body $O_2$ balance in exercising MI -10 days and -30 days after myocardial infarction. $V_0_2$, $O_2$ consumption. Data are mean±S.E.M.; *$P<0.05$ versus $0_L$, †$P<0.05$ -30 days versus -10 days (significant effect of time by two-way ANOVA).
Fig. 4. Regional blood flows in exercising MI −3 weeks after myocardial infarction. Data shown for N represent 0, 3 and 5 km/h; data shown for MI represent 0, 3 and 4 km/h. VO₂, O₂ consumption. Data are mean ± S.E.M.; *P < 0.05 versus 0, †P < 0.05 MI versus Normal (significant effect of infarction by ANCOVA). For the sake of clarity, symbols indicating a significant exercise-induced increase in skeletal muscle blood flow (which occurred at all exercise levels in all skeletal muscle groups for both MI and N) have been omitted.
responsiveness to circulating norepinephrine levels was blunted in MI compared to N, as higher levels of norepinephrine were required to produce the same level of heart rate and global LV contractility.

3.4. Cardiac anatomical data

Normalized right ventricular (RV) weight (RV to body weight ratio) was 47% higher in MI (1.62±0.20 g/kg) than in N (1.10±0.06 g/kg, \( P < 0.05 \)). Stepwise multivariate linear regression analysis showed that the degree of RV hypertrophy corresponded best with resting pulmonary artery pressure (\( r^2 = 0.81 \)), with no additional contribution of resting levels of endothelin, or of any other neurohormone. LV to body weight ratio was 3.63±0.15 g/kg in MI and 3.23±0.08 g/kg in N, representing a 12% increase (\( P < 0.05 \)). The degree of LV hypertrophy did not correspond with any of the hemodynamic determinants (e.g., left atrial pressure, \( r^2 = 0.15 \)) or resting levels of endothelin (\( r^2 = 0.10 \)) or norepinephrine (\( r^2 = 0.04 \)), but this may have been, at least in part, the result of the opposing effects of a large infarct on loss of viable tissue versus elevated loading conditions on the surviving myocardium.

3.5. Coronary circulation

In MI, the relations between myocardial \( O_2 \) consumption and myocardial \( O_2 \) extraction (ratio of \( O_2 \) consumption and \( O_2 \) supply) and between myocardial \( O_2 \) consumption and coronary venous \( Po_2 \) in the LV anterior free wall were shifted up- and downward, respectively, compared to those in N (Fig. 7), indicating that arterial \( O_2 \) supply was slightly impeded in MI. The impediment of blood flow occurred principally in the inner half of the LV wall, but was small and not associated with a widening of the arterio-coronary venous pH difference, suggesting that overt ischemia did not occur.

In the LV anterior free wall, arteriolar densities were similar in MI and N, while capillary densities were lower in MI (Fig. 8).

4. Discussion

This is the first study to investigate the integrated responses of LV pump function, neurohormones, and (regional) systemic, pulmonary and coronary hemody-
Fig. 6. Sympathetic responsiveness of the body and cardiac responsiveness to exercise-induced increases in norepinephrine in MI ~3 weeks after infarction. In the top right panel body VO$_2$ was expressed as a percentage of the estimated maximum body VO$_2$. In each pig, heart rate at the highest level of exercise was normalised as a percentage of 295 beats/min, which is the maximum heart rate for normal young pigs [6]. Since heart rate and body VO$_2$ as a percentage of maximum correlate closely during exercise, maximum body VO$_2$ was computed and all body VO$_2$ values were normalised as a percentage of the estimated maximum body VO$_2$. In MI, we previously observed that heart rates during exercise at 4 km/h in the presence of atropine did not increase above 260 beats/min. Consequently, we normalised heart rate at 4 km/h to the estimated maximum heart rate of 260 beats/min, and normalised body VO$_2$ accordingly. Data shown for N represent 0, 1, 2, 3, 4 and 5 km/h and for MI represent 0, 1, 2, 3 and 4 km/h. Mean data points were curve fitted with second order or third order (normal animals in the lower panels) curves. Data are mean±S.E.M. Symbols indicating significant differences versus resting (0) measurements have been omitted (see Figs. 1 and 5). *P<0.05 MI versus Normal (by ANCOVA).

4.1. Characteristics of LV dysfunction after myocardial infarction

4.1.1. LV dysfunction

LV dysfunction was produced by permanent ligation of the left circumflex coronary artery, which results in a circumscript transmural infarction of the lateral LV wall, comprising 20–25% of the total LV [10]. LV dysfunction in awake resting MI was characterised by 20–30% decrease in cardiac output, stroke volume and LV dP/dt$_{max}$ and a tripling of LV filling pressure (13±3 mmHg). Previously we observed that during the first week after infarction significant LV dilation occurs, but that between 1 and 6 weeks after infarction no further LV dilation occurs [8]. The present study shows that the difference between LV dP/dt$_{max}$, cardiac output and stroke volume in N and MI remained constant between ~10 and ~32 days, indicating that the degree of LV dysfunction and the circulatory adaptations in MI were stable during this observation period. In contrast, the global biventricular cardiomyopathy produced by 3–4 weeks of rapid ventricular...
Fig. 7. Myocardial blood flow and \( O_2 \) balance in the left ventricular anterior wall of N and MI 3 weeks after myocardial infarction. Epi, subepicardial; OM, outer mid; IM, inner mid; Endo, subendocardial; MVO\(_2\), myocardial \( O_2 \) consumption; and A-CV, arterio–coronary venous. In the top left panel data myocardial blood flow data are shown for resting (Rest, lying) conditions, and during maximum exercise (Ex, 5 km/h in N and 4 km/h in MI). Data are mean±S.E.M.; *\( P<0.05 \) versus 0, †\( P<0.05 \) MI versus Normal (by ANCOVA).

Pacing in dogs or pigs produces symptomatic and progressive heart failure (which is often reversible upon cessation of pacing, particularly during the initial stages of the process) that mimics severe end-stage human heart failure, reflected by 35–70% reductions in cardiac output and stroke volume [11–13], LV dP/dt\(_{max}\) [12,14], LV fractional shortening [12,13], and dramatic elevations in LV filling pressures (up to 30 mmHg [12–14]).

During exercise, cardiac output, LV systolic pressure and LV dP/dt\(_{max}\) increased almost in parallel in MI and N until 4 km/h, when curves began to diverge; 4 km/h was also the maximally attainable exercise level for most MI. In dogs with pacing-induced heart failure, exercise-induced increases in LV systolic pressure and LV dP/dt\(_{max}\) are even more reduced (up to 70%), reflecting the more severe degree of dysfunction [14].

4.1.2. Neurohumoral activation

Neurohumoral activation in resting MI was characterized by a trend towards elevated plasma levels of catechol-
amines but normal levels of the circulating renin–angiotensin–aldosterone system. The latter may have been due to the 50% increments in ANP and endothelin, which can suppress renin and aldosterone release [15]. In a recent study we observed that over a 6-week follow-up period in resting MI, ANP doubled within 24 h, recovered to 50% above normal values within 2 weeks and remained stable between 2 and 6 weeks after infarction, while renin and norepinephrine levels remained normal [8]. In contrast, the more severe hemodynamic abnormalities observed in pacing-induced heart failure are accompanied by marked neurohumoral activation including 4–20-fold elevations in plasma levels of catecholamines, renin, aldosterone and endothelin [13,16].

In contrast to the discrete neurohumoral activation in resting MI, exercise resulted in exaggerated increases in catecholamines and ANP and increases in endothelin, angiotensin II, and aldosterone. Patients with increasing severity of heart failure display a progressive blunting of the relative sympathetic drive [17]. While in the present study resting circulating levels of norepinephrine were still normal and the relative sympathetic drive in response to exercise was preserved in MI, the cardiac responsiveness to exercise (both heart rate and LV dP/dt max) was already blunted 3 weeks after infarction. A selective increase in cardiac sympathetic drive, which precedes generalized activation in heart failure patients [18], may have contributed to the blunted cardiac responsiveness to exercise-induced increases of norepinephrine, via β-adrenoceptor desensitization and/or downregulation.

4.1.3. Systemic circulation: O₂ transport and regional blood flows

Regional blood flows were slightly lower in visceral organs, under resting conditions and particularly during exercise, most likely due to the elevated catecholamine and endothelin levels. In contrast to the decreased skeletal muscle perfusion observed in rats [19,20], skeletal muscle blood flow was maintained in MI, both at rest and during exercise. Nitric oxide is particularly important in maintaining blood flow during exercise in slow oxidative and fast-oxidative but not in fast glycolytic muscle fibers [21], and because nitric oxide production is blunted in heart failure we hypothesized that a possible loss of nitric oxide would impair blood flow particularly in those muscle groups that contain the highest number of oxidative fibers (i.e., the deep red muscle) [22]. However, inspection of Fig. 4 shows that flows were maintained in all skeletal muscle groups, suggesting that either nitric oxide production is unperturbed at this stage of post-infarction LV dysfunction or that other vasodilators compensated. These results also suggest that skeletal muscle perfusion abnormalities do not contribute to the impaired exercise capacity early after MI, which supports rehabilitation starting early after infarction, when skeletal muscle perfusion and function are still normal.

MI were still capable of maintaining a normal body O₂ consumption, even during exercise, by increasing O₂ extraction as compensation for the lower cardiac output. In contrast, in pacing-induced heart failure cardiac output can decrease up to 70% [13], which simply cannot be compensated by an increased O₂ extraction, resulting in limited O₂ availability even under resting conditions.

4.1.4. Pulmonary circulation

Pulmonary artery pressure had almost doubled at ~3 weeks after infarction, which was associated with a 47% increase in RV weight. The increase in pulmonary artery pressure resulted from an increased left atrial pressure together with, at strenuous exercise-levels, a decrease in pulmonary conductance. The mechanism for the increased pulmonary tone cannot be determined from the present study, but could be due to loss of NO production. In addition, a role for endothelin is suggested by the inverse relation between endothelin concentrations and pulmonary conductance in resting pigs, which is in agreement with recent experimental and clinical heart failure studies [23]. The present study also shows that ~3 weeks following infarction, exercise-induced pulmonary vasodilation is virtually absent in MI, possibly due to the exercise-induced increase in endothelin levels.

4.2. Coronary circulation

Marked decreases in myocardial perfusion occur in pacing-induced severe heart failure in pigs [24] and dogs [14,25], especially in the more vulnerable subendocardial layers. Although one study in dogs indicated that the lower myocardial blood flow is principally the result of a lower myocardial Vo₂ [14], studies in pigs suggest that the impaired perfusion is responsible for the deterioration of LV function because the ultrastructural changes resemble those that are associated with ischemia (i.e., interstitial edema and disruption of collagen fibers in the subendocardium) [26,27]. In animals models of compensated pressure – overload – induced severe LV hypertrophy, selective underperfusion of the subendocardium can produce myocardial ischemia during exercise and result in post-
exercise myocardial stunning [9,28,29]. Repetitive exercise-induced stunning may lead to progressive functional and structural ischemic changes contributing to the deterioration of LV function over time [28,29].

The contribution of perfusion abnormalities in the remote surviving myocardium after a myocardial infarction to the LV dysfunction remains unclear. Studies in rats [1,2] demonstrated a 25–40% reduction in coronary flow reserve in the surviving myocardium at 4 [1] and 8 [2] weeks after myocardial infarction. In addition, maximum subendocardial blood flow was limited by 40% in anesthetized pigs with heart failure 3 weeks after a myocardial infarction [3].

We hypothesized that the decreased flow reserve could limit the increase in myocardial blood flow to the hypertrophied myocardium during exercise when hemodynamic abnormalities and neurohumoral activation are exacerbated, thereby impairing myocardial O₂ supply. LV filling pressures were elevated in MI (to a similar level as in the study of Zhang et al. [3]), while endothelin and norepinephrine levels were increased, particularly during exercise.

Three weeks after infarction, myocardial blood flow per gram of tissue in the LV anterior wall of resting MI, was similar to that in resting N, confirming previous studies in rats and pigs [1–3]. In contrast, during the initial 14 days after infarction, an increase in basal flow per gram of myocardium in the remote surviving part of the LV has been reported [30], which most likely reflects the increased myocardial metabolic demands at a time when LV dilation is present [8] but hypertrophy is still in progress. Interestingly, we observed a small trend towards higher blood flows in the outer two layers (P=0.09), suggesting that despite hypertrophy of the surviving myocardium [8], metabolic demand per gram of myocardium in the outer, but not the inner, layers was still slightly elevated, 3 weeks after infarction. The LV to body weight ratio increased by only 12%, suggesting that LV hypertrophy in response to the volume-overload (in contrast to the 47% increase in RV to body weight ratio secondary to the 75% increase in pulmonary artery pressure) was only modest. However, the LV to body weight ratio likely underestimates the degree of hypertrophy in the surviving portion of the LV myocardium, due to the loss of 20–25% of viable LV myocardium and replacement by scar tissue. Consequently, based on previous observations from our laboratory, the degree of hypertrophy of the surviving portion of the LV was more likely in the range of 25–30% [4].

During exercise, myocardial blood flow increased but was distributed away from the subendocardium towards the subepicardium in MI compared to N. The impedance of subendocardial blood flow and hence O₂ supply in MI, necessitated a small increase in O₂ extraction which resulted in a lower coronary venous P O₂. This effect was only small, although lower myocardial capillary density may have prevented a greater increase in O₂ extraction and a further lowering of coronary venous P O₂ in MI compared to N. On the other hand, the arterio–coronary venous pH difference was similar to N, suggesting that anaerobic metabolism was absent and that myocardial blood flow and O₂ consumption were still matched up to exercise levels at 85% of maximum heart rate. These findings indicate that despite increases in extravascular forces (elevated LV filling pressures), increased circulating levels of catecholamines and endothelin and possibly loss of NO production, there is sufficient coronary vasodilator reserve to maintain myocardial blood flow commensurate with metabolic needs.

### 4.3. Clinical relevance

The present study indicates that 3 weeks after myocardial infarction, LV dysfunction is clearly present evidenced by hemodynamic abnormalities and neurohumoral activation at rest and particularly during exercise, but that myocardial blood flows are only slightly impaired leaving myocardial O₂ consumption unaffected. The lack of overt anaerobic metabolism even during heavy exercise suggests that myocardial perfusion abnormalities within the surviving myocardium do not contribute to LV dysfunction in the first few weeks after infarction. This also suggests that patients with a recent myocardial infarction can safely perform light to moderate exercise (<75% of maximum heart rate) without an increased risk of encountering myocardial ischemia, provided there is no significant coronary artery disease within the non-infarcted myocardial regions, and supports increasing efforts to initiate rehabilitation early after myocardial infarction as a therapeutic adjuvant to prevent deconditioning and progression of LV dysfunction [31]. This study was in part supported by a grant from E. Merck Darmstadt.

### Acknowledgements

Rene Stubenitsky, Angelique van den Heuvel and Rob van Bremen are gratefully acknowledged for technical assistance. The research of Dr. Duncker has been made possible in part by a Research Fellowship of the Royal Netherlands Academy of Arts and Sciences, and an ‘Established Investigator’ stipend of The Netherlands Heart Foundation (2000D038).

### References

al. Functional and bioenergetic consequences of postinfarction left ventricular remodeling in a new porcine model. MRI and 31 P-MRS study.


