Regular Article

Functional mechanisms of myocardial microcirculation in left ventricular hypertrophy

A hypothetical model of capillary remodeling post myocardial infarction

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Abstract

Objectives: Left ventricular (LV) remodeling after myocardial infarction (MI) is characterized by myocyte hypertrophy and a disproportional capillary growth. We developed a hypothetical model of capillary remodeling mechanisms based on quantitative data of microcirculation determined by magnetic resonance (MR) imaging techniques and histology.

Methods: Perfusion and regional capillary blood volume (RBV) were quantified 8 and 16 weeks after MI (mean 27.0±2.9% of the left ventricle 16 weeks post MI) or sham operation in rats using MR imaging and were correlated with morphometric data.

Results: Maximum perfusion (ml/(g min)) in the remote area decreased from 5.69 ±0.63 to 3.48 ±0.48 compared to sham animals (5.33±0.31, p ≤ 0.01) and showed a close inverse relation to hypertrophy. In contrast, maximum RBV in the remote area was similar to that of sham animals (16.79±0.42% and 16.52±0.33%, respectively) and did not change over time. Thus, mean transit time (MTT) was longer in remote than in sham myocardium. Morphology revealed that hypertrophy was inversely related to capillary density which was associated with an increase in capillary cross-sections.

Conclusions: Perfusion data in synopsis with histological observations demonstrate that the functional capillary length increases during hypertrophy post MI which is consistent with the increase of the mean transit time. Despite a relative decrease in capillary density, RBV may be restored by an increase in the cross-sections. In the light of almost maximum oxygen extraction under normal conditions, this hypertrophy related remodeling may be deleterious for tissue supply.

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Introduction

Tissue loss after MI results in remodeling of the surviving myocardium with reactive myocyte hypertrophy (Pfeffer et al., 1979; Anversa et al., 1985). Morphometric studies revealed a disproportional growth of capillaries compared to the increase of myocyte cross-sectional areas (Xie et al., 1997) and, hence, an increase of the diffusion distance for oxygen (Anversa et al., 1986).

Whereas the quantitative determination of capillary density is well established, assessment of the capillary length is more complex. Depending on an anatomical or functional point of view one distinguishes the length of a single capillary from its functional length. The first refers to the distance between arteriolar and venular cross-connections and is about 90 μm in the normal rat myocardium (Batra and Rakusan, 1990). The functional length is the distance between adjacent arteriolar and venular domains, i.e. it reflects the way blood flows from the arteriolar to the venular zone (Beard and Bassingthwaighte, 2000) and is about 600 μm (Batra and Rakusan, 1990). Thus this definition considers the capillary as a hemodynamic unit within the capillary network and it directly corresponds to the supply function of a capillary. Morphometric...
analysis in the hypertrophied rat heart revealed that the functional mean length was significantly longer compared to normal hearts (Batra et al., 1991).

However, it would be of paramount interest to correlate these morphological observations to functional non invasive data of microcirculation in order to assess its potential consequences for remodeling of myocardium. Recently, new magnetic resonance imaging (MRI) techniques have been developed for the quantitative measurement of myocardial perfusion and intracapillary blood volume (RBV) in the healthy rat heart (Kahler et al., 1999; Waller et al., 2000) and in rat hearts during chronic left ventricular remodeling after myocardial infarction (Waller et al., 2001). As an additional parameter of microcirculation the mean transit time (MTT) of blood within the capillary system may be determined as MTT = RBV/perfusion. Obviously this parameter corresponds to the functional capillary length.

The aim of the present study was to determine functional microcirculation in the remote myocardium during left ventricular (LV) remodeling using MRI and to correlate these data with morphometric analysis of the same tissue. From these data, a hypothetical model of capillary remodeling has been developed to elucidate the functional mechanisms of blood supply during LV remodeling. We anticipated that in hypertrophied LV myocardium, functional length of capillaries and hence, MTT, increases. As it is known from basic physiology of the coronary microcirculation, the oxygen extraction along the capillary length is of about 70–75% even under normal conditions. This cannot be further increased without jeopardizing the average intracellular oxygen pressure. Hence, an increase of capillary length in accordance with an increase of MTT in post infarction hypertrophy could result in a lack of oxygen supply.

Methods

Animal preparation

All experimental procedures with animals conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and were approved by the local authorities. In adult female Wistar rats (Charles River, Sulzfeld, Germany, 250–290 g) myocardial infarctions were produced using a method described previously (Pfeffer et al., 1979). After oral intubation under ether anesthesia, left thoracotomy was performed and the pericardium was incised. The heart was exposed and the left coronary artery (LCA) was ligated. After reposition of the heart, the thorax was instantly closed. Animals recovered during the following 24 h after surgery. Mortality was 38% within this time period. In sham-operated rats, the ligature around the LCA was not tied and all animals survived after surgery.

For MR measurements, animals were anesthetized with sodium pentobarbital (Narcoren, Rhone Merieux GmbH, Laupheim, FRG; 40 mg/kg i.p.), were orally intubated and ventilated by a small rodent respirator (BAS-7025, FMI, FRG, covering the posterior, lateral and septal left ventricular regions remote from the infarct (160–180 pixels) was selected as region of interest (ROI). In the sham-operated group, a mid-myocardial ROI covering the whole left ventricle (210–250 pixels) was manually delineated. Mean values for perfusion and RBV were obtained by averaging the pixel data in the ROI. Mean capillary transit time

MR imaging and data analysis

MRI of myocardial perfusion and relative intracapillary blood volume

All images were acquired on a 7.05-T Biospec 70/21 spectrometer (Bruker). A specially adapted double probe head for rat heart measurement was used (Rapid Biomedical, Germany). Quantitative T1 measurements were acquired by using an inversion recovery snapshot fast, low-angle shot (FLASH) sequence (Haase et al., 1990). Twenty-four ECG-triggered snapshot FLASH images were recorded after global or slice-selective spin inversion. Each snapshot FLASH image (TR=2.25 ms, TE=1 ms, flip angle about 3°, slice thickness 3 mm, field of view 50×50 mm) had a spatial resolution in plane of 390×780 μm2. Total acquisition time for one T1 experiment was in the range of 2×24=48 FLASH images (1–2 min). Images were obtained in a short axis slice perpendicular to the long axis of the left ventricle 4–6 mm below the valvular plane. Infarcted myocardium was regularly visible in the imaging slice. Blood flow was measured with a slice-selective and a global T1 experiment, RBV was determined by slice-selective T1 experiments before and after application of Gd-DTPA-albumin. The acquisition time for four perfusion or RBV maps was about 15 min. The duration of the whole perfusion or RBV measurement was therefore about 30–35 min. Values for T1 in the blood of global T1 experiments before and after CA were 1.61±0.05 s and 0.52±0.03 s, respectively. The calculated RBV has to be corrected by a factor which is determined by the ratio of hematocrit in the ventricle and the capillaries. Since hematocrit (Hct) of the capillary blood is 63–75% of the blood of larger vessels the ratio is found to be (1−Hctcapillaries)/(1−Hctventricles) = 1.34. Further methodological details are described elsewhere (Belle et al., 1998; Bauer et al., 1997).

MR cine imaging

An ECG-triggered fast-gradient echo sequence (FLASH) (Haase et al., 1990) was performed with a flip angle of 40°, echo time of 1.2 ms and a repetition time of 4.3 ms. 16 contiguous ventricular short-axis slices of 1 mm thickness with no interslice gap were acquired to cover the entire range of the ventricles. With a field of view of 30–35 mm and an acquisition matrix of 128×128, the resolution in-plane was 270×310 μm2. Depending on heart rate, acquisition time for one cine image was in the range of 40 to 50 s. Signal-to-noise ratio (SNR) was increased by averaging the images four times.

Data analysis

For quantification of perfusion and RBV, a mid-myocardial region in the surviving myocardium of the infarcted animals covering the posterior, lateral and septal left ventricular regions remote from the infarct (160–180 pixels) was selected as region of interest (ROI). In the sham-operated group, a mid-myocardial ROI covering the whole left ventricle (210–250 pixels) was manually delineated. Mean values for perfusion and RBV were obtained by averaging the pixel data in the ROI. Mean capillary transit time
(MTT) was calculated as the quotient of RBV and perfusion. Myocardial and ventricular volumes were determined from end-diastolic and end-systolic images in all slices by multiplication of compartment area and slice thickness. Total volumes were calculated as the sum of all slice volumes. LV mass was calculated as LV end-diastolic myocardial volume multiplied by the myocardial-specific gravity (1.05 g/cm³).

Hemodynamics in vivo

A terminal hemodynamic study was performed 16 weeks after sham operation or coronary artery ligation following the MR experiments. In addition, hemodynamic studies were performed in 16 animals with either 8 weeks old MI (n=8) or sham operation (n=8). A polyethylene catheter (Portex, Kent, Great Britain) connected to a Millar micromanometer (Millar Instruments, Houston, USA) was used to measure the mean aortic pressure (MAP) and heart rate (HR). Hemodynamic data were recorded at rest and during infusion of adenosine following the experimental setup of the MR experiments. Coronary resistance was calculated from mean aortic pressure in mm Hg and MR perfusion data in ml/g/min according to CR = mean aortic pressure/blood flow. This is allowed since the left ventricular end-diastolic pressure (LVEDP) was shown to remain comparable to sham values in animals with small to moderate infarct sizes 8 and 16 weeks after operation (Nahrendorf et al., 2003; Hu et al., 1998).

Histology and immunohistochemistry

Hearts were perfused with purified water and fixed in paraformaldehyde and then sectioned perpendicular to the longitudinal axis. Three adjacent sections, ≈8 mm thick, were obtained distal to the ligature from the base to the apex. Quantitative analyses were performed using a microscope (Carl Zeiss, Göttingen, Germany) equipped with an imaging software (Visitron Systems, Puchheim, Germany). Hematoxylin and eosin were used for measuring infarct size following a method described by Pfeffer et al. (1979), and cross-sectional myocyte areas. Sections in the short-axis view approximately covering the MR imaging slice were stained on paraffin embedded heart tissue with lectin GS I (griffonia simplicifolia I, Sigma, Bonn, Germany) which is a specific endothelial cell marker (Kuizinga et al., 1992). Visual fields (VF) of transversely sectioned capillaries and muscle fibers were selected at ×32 magnification in the mid-myocardial regions in the remote area of the infarcted animals (20–30 VF) and in the sham animals (20–30 VF). In each VF, 15 to 20 myocytes were manually delineated for the determination of cross-sectional areas. Capillary densities and cross-sectional areas were quantified automatically using a color and magnitude threshold.

Experimental protocol

MRI experiments were performed on 8 animals with myocardial infarction, 6 animals were sham-operated controls. Animals were examined serially at 8 and 16 weeks after operation. At each time point, the following measurements were performed: MR perfusion at rest, MR perfusion during adenosine, MR intracapillary blood volume during adenosine, after withdrawal of the drugs MR intracapillary blood volume at rest and cine imaging. At 16 weeks, final hemodynamic measurements of all animals were performed after MR measurement. Finally, hearts were removed and used for histological staining. Due to the serial character of the study, two additional groups were introduced to perform hemodynamic studies 8 weeks after MI or sham operation.

Statistical analysis

The data are expressed as mean±SEM. Statistical comparisons among the groups were evaluated by ANOVA and significant difference was determined by Tukey–Kramer’s test. P<0.05 was considered to indicate statistical significance. Linear regression analysis was performed between the capillary density (expressed as capillaries per mm²) and the myocyte cross-sectional area (expressed as μm²) and the capillary cross-sectional area (expressed as μm²), respectively, for the sham-operated group and the infarcted animals. Additionally, linear correlation between the myocyte cross-sectional area (expressed as μm²) and the coronary resistance (expressed as mm Hg g min/ml) for the remote area of the infarcted animals at rest and during vasodilatation was determined.
Results

Perfusion and intracapillary blood volume during LV remodeling

Perfusion and RBV maps of a representative heart from an animal 8 weeks after induction of myocardial infarction (MI size 27% of the LV area) at rest and during infusion of 3 mg/(kg min) of adenosine are shown in Fig. 1A. Corresponding maps of perfusion and RBV of a sham-operated animal (group 2) at rest and during vasodilatation are illustrated in Fig. 1B. The scar is visible in the anterior myocardial wall. The remote hypertrophied portions of the left ventricle are clearly distinct in the perfusion and RBV maps.

MI size ranged from 17.6% to 47.8% (mean of 32.5±3.6%) of the LV area, determined 16 weeks after operation. Quantitative MR data for perfusion (in ml/(g min)) and RBV (in %) of the remote myocardium of the infarcted animals and the sham-operated group are shown in Table 1a, b.

LV volumes and mass during LV remodeling

In the infarcted animals, LV mass was significantly increased from 8 (544±23 mg) to 16 weeks (682±39 mg) (p≤0.01). LV mass of the sham-operated animals at 8 weeks was 528±47 mg and at 16 weeks 547±45 mg (p≤0.01 compared to the group 16 weeks post MI). LV end-diastolic volumes of the infarcted group were unchanged from 8 weeks (533±55 μl) to 16 weeks (506±47 μl), however, were significantly elevated (p<0.01) compared to the sham animals (142±11 μl at 8 weeks and 174±12 μl at 16 weeks). LV end-systolic volumes of the animals with MI were 384±39 μl and 376±36 μl at 8 and 16 weeks, respectively. These values were significantly different from end-systolic volumes of the sham animals at 8 weeks (60±8 μl, p<0.001) and 16 weeks (86±10 μl, p<0.01). Body weight of the infarcted animals were 291±7 g at 8 weeks and 315±4 g at 16 weeks. Sham-operated animals had body weights of 290±10 g and 314±9 g at 8 and 16 weeks, respectively.

Morphometric analysis during LV remodeling

Myocyte areas (in μm²) in the remote myocardium at 8 weeks (333±14) increased to 450±24 at 16 weeks post MI (p<0.01) and were elevated compared to the sham-operated animals at 8 (306±14, p<0.05) and 16 weeks (305±25, p<0.01). Capillary densities (in no./mm²) in the remote area were 3359±134 at 8 weeks after MI and decreased to 2955±177 at 16 weeks after

Table 1
Quantitative MR for (a) perfusion data (ml/(g min)) and (b) RBV data (%)

<table>
<thead>
<tr>
<th></th>
<th>Myocardial infarction (MI)</th>
<th></th>
<th>Border zone</th>
<th></th>
<th>Sham</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>At rest</td>
<td>Adenosine</td>
<td>At rest</td>
<td>Adenosine</td>
<td></td>
</tr>
<tr>
<td>(a) 8 weeks</td>
<td>4.13±0.22</td>
<td>5.69±0.63</td>
<td>2.81±0.11</td>
<td>3.73±0.23</td>
<td>3.40±0.19</td>
</tr>
<tr>
<td>16 weeks</td>
<td>2.73±0.23</td>
<td>3.48±0.48</td>
<td>1.98±0.18</td>
<td>2.54±0.15</td>
<td>3.21±0.23</td>
</tr>
<tr>
<td>(b) 8 weeks</td>
<td>11.49±0.45</td>
<td>16.79±0.42</td>
<td>8.57±0.33</td>
<td>13.87±0.64</td>
<td>8.81±0.15</td>
</tr>
<tr>
<td>16 weeks</td>
<td>12.47±0.59</td>
<td>15.95±0.34</td>
<td>8.81±0.38</td>
<td>11.41±0.76</td>
<td>8.44±0.19</td>
</tr>
</tbody>
</table>

a p≤0.01, remote area vs. border zone.
b p≤0.01, 8 weeks vs. 16 weeks.
c p≤0.01, 8 weeks MI vs. Sham.
d p≤0.01, 16 weeks MI vs. Sham.
MI. In sham-operated animals, capillary densities were 3460±81 at 8 weeks and 3594±113 at 16 weeks post operation (p<0.05 16 weeks MI vs. Sham). Capillary cross-sectional areas (in μm²) 8 weeks after MI in the remote myocardium were 12.4±1.1 and increased to 18.6±1.9 at 16 weeks (p<0.01). Sham animals had capillary cross-sectional areas of 13.0±1.5 and 12.7±1.0 at 8 and 16 weeks after operation, respectively (p<0.01 16 weeks MI vs. Sham). Linear regression analysis of capillary density and myocyte area during the observation time for the remote area of the infarcted animals are shown in Fig. 2(a). A significant correlation was found between both parameters. Linear regression analysis of capillary cross-sectional areas (remote and sham myocardium) and capillary density demonstrates an inverse relationship between both parameters which is illustrated in Fig. 2(b).

**Coronary resistance and mean transit time**

In the animals with MI, infarct size (in %) was comparable in both groups (27.9±3.5 at 8 weeks post MI and 29.0±2.4 at 16 weeks post MI). Mean aortic pressure (MAP, in mm Hg) at rest was 111.3±3.7 at 8 weeks and 109.6±2.3 at 16 weeks after MI compared to the sham animals (110.6±2.2 and 115.9±2.0 at 8 and 16 weeks, respectively). During vasodilatation, MAP decreased significantly (p<0.01) in the infarcted animals (43.2±2.4 at 8 weeks and 44.0±2.1 at 16 weeks) and in the sham-operated groups (50.2±2.5 and 51.1±3.0 at 8 and 16 weeks, respectively). Heart rate (in beats/min) was comparable in all groups at rest (358±20 and 343±21, 8 and 16 weeks post MI, and 360±20 and 369±14, 8 and 16 weeks after sham operation) and decreased significantly during vasodilatation (p<0.01) (182±19 and 175±16, 8 and 16 weeks post MI, 197±15 and 219±20, 8 and 16 weeks after sham operation). There was a significant positive correlation between CR and the myocyte areas in the remote myocardium at rest and during vasodilatation (Fig. 3).

Data of the MTT analysis are shown in Fig. 4. MTT increased from 8 to 16 weeks in the whole myocardium of the animals with MI and was significantly higher at 16 weeks than that in the sham-operated group (p≤0.001).

**Discussion**

Chronic myocardial infarction results in left ventricular hypertrophy and consecutive changes in microvascular network (Anversa et al., 1986; Batra et al., 1991; Rakusan et al., 1980). Studies of our group revealed significant changes of perfusion and RBV in hypertrophied myocardium post myocardial infarction determined by MRI (Waller et al., 2001). However, the underlying adaptive mechanisms at microvascular level are unclear. Therefore, from functional data of perfusion and RBV obtained by MR imaging and morphological data in the same animal, we derive a hypothetical model of capillary remodeling which describes the adaptive processes during LV hypertrophy which implies an increase in capillary cross-section and functional capillary length of a single capillary. These findings are in accordance with an increase in mean transit time in hypertrophied myocardial tissue.

**Model of capillary remodeling**

We found that the maximum RBV in the remote area was comparable to that of sham animals and it did not change over time. Since remodeling of remote myocardium implies a hypertrophic response, the RBV_max appears to be independent from the degree of hypertrophy. However, capillary density was inversely related to hypertrophy. These, at a first glance, controversial findings become congruent by considering the cross-sectional area of a single capillary. We assumed that this cross-section is proportional to the capillary diameter². Hence, regression analysis in Fig. 2(b) and morphometric data demonstrate that the reduction of capillary density is in part compensated by an increase in capillary cross-section. This may explain the
independence of the functional parameter RBV$_{\text{max}}$ from hypertrophy. This is illustrated in the cross-sectioned myocardium in Fig. 5(a, b). Maintenance of maximum capillary blood volume implies an increase in the mean capillary cross-section when capillary density decreases due to left ventricular hypertrophy. In contrast to that, the functional parameters perfusion and vascular resistance declined with increasing hypertrophy. The capillary conductance $C_{\text{max}}$ after vasodilatation satisfies

$$C_{\text{max}} \sim c \times d^4 \times l^{-1} \quad (1)$$

where $c$ is the capillary density, $d^4$ is the fourth power of the capillary diameter and $l$ is the average functional capillary length.

The maximum RBV may be described as

$$\text{RBV}_{\text{max}} \sim c \times d^2 \quad (2)$$

Hence, one can write

$$C_{\text{max}} \sim \text{RBV}_{\text{max}}^2 \times c^{-1} \times l^{-1} \quad (3)$$

Since increase of capillary cross-section maintains RBV$_{\text{max}}$ almost constant during remodeling, sole reduction of capillary density should result in an increase of conductance. Since during vasodilatation the capillary conductance clearly dominates the total vascular conductance (Jayaweera et al., 1999), the latter should also increase. However, the opposite was observed in our experiments. According to Eq. (3), this observation can be explained by an increase in functional capillary length which is illustrated in the longitudinal sectioned myocardium of Fig. 6(a, b). The increase of the functional capillary length during hypertrophy (hyp) related to sham may be estimated from Eq. (3) as

$$\frac{C_{\text{max, hyp}}}{C_{\text{max, sham}}} = \left( \frac{\text{RBV}_{\text{max, hyp}}}{\text{RBV}_{\text{max, sham}}} \right)^2 \times \left( \frac{c_{\text{sham}}}{c_{\text{hyp}}} \right) \times \left( \frac{l_{\text{sham}}}{l_{\text{hyp}}} \right) \quad (4)$$

The ratio of the conductances is given by that of the corresponding maximum perfusion values, since other hemodynamic parameters did not differ between sham and infarcted animals, i.e. $C_{\text{max, hyp}}/C_{\text{max, sham}} = 3.48/5.33 = 0.65$ (see Results), the ratio of the maximum capillary blood volumes is approximately 1, and that of the capillary densities may be depicted from morphometric data as $C_{\text{sham}}/C_{\text{hyp}} = 1.22$, i.e. one obtains

$$l_{\text{sham}}/l_{\text{hyp}} = 0.53, \quad (5)$$

or in other words, 16 weeks of development of hypertrophy doubles the functional length of a capillary. When we look at the mean transit time, one obtains for resting conditions

$$\frac{\text{MTT}_{\text{sham}}}{\text{MTT}_{\text{hyp}}} = 1.49/2.77 = 0.54 \quad (6)$$

i.e. the mean transit time doubles as the functional length during hypertrophy. These findings match excellently when we assume that the intracapillary blood velocity $l/\text{MTT}$ does not change during remodeling.

It is important to stress that the hypothesis that the functional capillary length almost doubles during 16 weeks of remodeling is supported by two different considerations: the first combines histological with functional data during vasodilation (Eqs. (1)–(5)), the second employing the mean transit time is solely derived from functional data under resting conditions (Eq. (6)).

Mean transit time during left ventricular remodeling

The MTT is a parameter which is calculated from the ratio RBV/blood flow per volume tissue (perfusion) and determines the time spent by the blood traversing the microcirculation. Only few data are available which focus on the analysis of MTT in healthy animal hearts (Allard et al., 1993; Rose and Goresky,
whereas no study today has determined MTT in a heart with left ventricular remodeling following chronic MI. Our data reveal that MTT is increased in hypertrophied myocardium which is due to an increase in the functional length of the capillaries. However, since oxygen extraction along the capillary length reaches a maximum even in normal myocardial tissue an increase in MTT and an increase in functional capillary length implies that towards the venous end of the capillary there is no sufficient oxygen delivery from the capillary to the surrounding tissue. Therefore one can speculate that the increase in MTT and functional capillary length during development of left ventricular hypertrophy may be responsible for potential ischemia especially under stress conditions and may aggravate LV remodeling. Data of several groups may confirm this speculation since an increase in programmed myocyte cell death was regularly found in the viable remote rat myocardium late after infarction (Cheng et al., 1996; Palojoki et al., 2001). It has to be stressed that this mechanism of microvascular mal-adaptation has not been considered in the past yet and differs from the usually considered increase of oxygen diffusion distance which is related to the decrease of capillary density.

**Conclusion**

Chronic myocardial infarction and left ventricular hypertrophy result in significant changes in microvascular network. Whereas perfusion changes are correlated with LV hypertrophy, maximum regional capillary blood volume appears to be independent from that. Reduction of capillary density relative to hypertrophy is accompanied by an increase in cross-sectional area, functional capillary length of the single capillary and thus MTT. Whereas the increase of the cross-section may compensate in part the decrease of capillary density, the increase of functional length and mean transit time may hamper sufficient supply of the myocytes. Hence, the decrease of capillary density with consecutive increase of functional length and mean transit time in the hypertrophied residual myocardium may be factors leading to a progression of LV remodeling after myocardial infarction.

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