Recovery mismatch between myocardial blood flow and cardiac workload after physical exercise: a positron emission tomography study

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Aims
We studied the interrelation between oxygen consumption and myocardial blood flow (MBF) during recovery. MBF is directly dependent on oxygen consumption. The latter is linearly related to the heart rate–blood pressure product (RPP, bpm × mmHg), an index reflecting external cardiac work. In the immediate post-exercise period, cardiac output decreases considerably. This is expected to be paralleled by a rapid fall in oxygen demand, rendering ischaemia unlikely. Thus, the phenomenon of ST-segment depression during recovery remains unexplained.

Methods and results
¹⁵O-labelled water and positron emission tomography were used to measure MBF in 14 young healthy volunteers (mean age 27 ± 3 years) during the following study conditions: (i) at rest, (ii) during a steady submaximal supine bicycle exercise stress within the scanner, and (iii) during recovery immediately after cessation of exercise. During recovery, RPP decreased by 43% (18 768 ± 1337 vs. 11 652 ± 3224, P < 0.001). In contrast, the associated decrease in MBF (2.52 ± 0.52 vs. 1.93 ± 0.50 mL/min/g, P < 0.001) and perfusion reserve (2.68 ± 0.51 vs. 2.03 ± 0.42, P < 0.001) was significantly less pronounced (−24%, P < 0.01), indicating a relative delay in MBF recovery compared with cardiac work load.

Conclusion
The mismatch between a rapid decrease in cardiac workload but preserved hyperaemic response early after cessation of physical exercise suggests an uncoupling of cardiac work and MBF during recovery.

Keywords
PET • Myocardial blood flow • Physical exercise • Recovery

Introduction
Myocardial blood flow (MBF) is directly dependent on oxygen consumption. The latter is linearly related to the heart rate–blood pressure product (RPP), an index reflecting external cardiac work.¹ In fact, as an increase in MBF has been documented with an increased RPP at rest,² it has been generally suggested to normalize resting MBF for a predefined RPP in order to allow meaningful comparison between measurements at different haemodynamic conditions.³–⁷ This is even more pronounced in high demand situations such as increased oxygen consumption during physical exercise.⁶–⁹ Conversely, MBF has been reported to decrease in response to a decline in RPP following administration of beta-receptor antagonists.¹⁰ Little is known, however, about the time course of the decrease in MBF and its relation to the changing RPP during recovery, when the workload on the heart and heart rate (HR) are known to fall rapidly. As the rapid decline in RPP is supposed to be paralleled by a decrease in oxygen consumption, the occurrence of an oxygen demand-supply mismatch causing ischaemia appears unlikely under such conditions. Nevertheless, ischaemic ST-segment depression that begin during recovery period have been described in a substantial proportion of patients undergoing treadmill exercise. In fact, a diagnostic and prognostic significance of such ECG changes similar to ST-segment depression occurring during exercise has been documented. However, the underlying pathophysiological mechanism(s) causing ST-segment changes during recovery remain(s) an unsettled issue.¹¹–¹⁵ We
hypothesized that, at early recovery, the rapidly decreasing cardiac work and the related oxygen consumption may not be paralleled by a rapid decrease in MBF, indicating a shift of the oxygen demand-supply curve. Therefore, the aim of the study was to assess the physiological time course of MBF at recovery and to compare this with the rapid decline in RPP after exercise in young healthy volunteers.

**Methods**

**Study population**
Fourteen young healthy volunteers (mean age 27 ± 3 years) were consecutively enrolled in our study within 2 months. Four subjects were female and none of the study participants had a history of cardiovascular disease. Inclusion criteria were a normal resting ECG, normal HR, normal blood pressure, no history of heart disease or excessive endurance training, and an unremarkable exclusive cardiopulmonary examination. Additionally, study participants had to have no history of smoking and were asked to refrain from caffeine intake for 24 h before the study as previously suggested. All female study participants had a negative urine pregnancy test. The study protocol conforms with the principles outlined in the Declaration of Helsinki, was approved by the local ethics committee, and all patients gave written informed consent prior to enrolment.

**Study protocol**
First, MBF was measured at rest. After allowing for decay of 15O-labelled water, exercise was begun at 50–75 W and workload was increased in increments of 25–50 W until a strenuous workload was reached (mean workload 109 ± 18 W). The first hyperaemic MBF measurement was performed 1 min after a steady strenuous workload was achieved. The pedalling rate was 50–55 rpm. Such a low pedalling rate was chosen in order to minimize the body motion during positron emission tomography (PET) scanning. Volunteers had to maintain the workload throughout the scan time (4 min and 40 s) and for another 5 min to allow for decay of 15O radioactivity in the body before the second hyperaemic MBF measurement was assessed non-invasively with a brachial cuff and recorded every minute, along with ECG and HR. Averaged haemodynamic values were provided in Table 1. Exercise caused a significant increase in mean MBF to 2.52 ± 0.52 mL/min/g (168%, P < 0.001) after cessation of exercise, i.e. during recovery. Haemodynamic measurements were continued for 5 min during recovery in order to cover the scan time. Blood pressure was assessed non-invasively with a brachial cuff and recorded every minute, along with ECG and HR. Averaged haemodynamic values were used where appropriate to represent an integration over the scan time.

**Image acquisition**
PET image acquisition was performed in the PET Center of the University Hospital of Zurich on a GE Advance Scanner (GE Healthcare). This device records 35 image planes simultaneously in a 2D mode. The axial field of view is 14.5 cm. A 30-min blank scan was recorded as part of the daily routine. For attenuation correction, a 20-min transmission scan using an external 44Ge source was performed. Starting after the background frame, a dose of 600–700 MBq of 15O-water was injected as intravenous bolus over 20 s at an infusion rate of 24 mL/min to assess MBF. The dynamic image sequences obtained were 14 × 5, 3 × 10, 3 × 20, and 4 × 30 s. The total radiation dose of the study accounts to ~2.5 mSv.

**Image processing**
The sinograms obtained were corrected for attenuation and were reconstructed on a dedicated workstation (SUN Microsystems, Mountain View, CA, USA) using standard reconstruction algorithms. Images were analysed with a pixelwise modelling software developed and validated at our institution (PMOD; www.pmod.com). Myocardial images were then generated directly from the dynamic 15O-water study, avoiding the need for additional 15O-carbon monoxide blood pool scans to define regions of interest as previously reported.16,17 Regions of interest were drawn within the left ventricle to generate blood time–activity curves (input function), and onto the right ventricle, to correct for spill-over in the septum. Similarly, myocardial regions of interest were drawn within the left ventricular myocardium to obtain tissue activity curves. The junctions of right and left ventricles were marked to indicate the septum. Arterial and tissue activity curves were fitted to a single-tissue compartment tracer kinetic model to give values of global MBF (mL/min/g), as has previously been described.18

**Data interpretation**
The absolute and percent increase in MBF from rest to exercise and to recovery was calculated. To account for the variability of coronary driving pressure, the ratio of mean arterial pressure to MBF was calculated as an index of as previously described.19,20 Coronary flow reserve (CFR), which is an integrated parameter of endothelial function and vascular smooth muscle relaxation, was calculated as the ratio of hyperaemic to resting MBF.

**Statistical analysis**
Numerical values are given as mean ± SD. We assessed the changes (delta) in MBF, CFR as well as haemodynamic parameters, and coronary resistance values. Statistical comparison of delta MBF, delta CFR, delta RPP values, and delta coronary resistance values was performed using the ANOVA statistics for repeated measurements with the Bonferroni post hoc analysis. P-values < 0.05 were considered statistically significant.

**Results**
All bicycle exercise procedures were well tolerated and no subjects had to be withdrawn from the analysis. None of the subjects experienced any significant ECG changes or unphysiological alterations of blood pressure and all resting parameters were within normal limits.

**Haemodynamics**
Data of haemodynamic variables throughout the study protocol are provided in Table 1. Exercise caused a significant increase in systolic blood pressure (SBP) by 31%, HR by 111%, and RPP by 188%, compared with rest (all P < 0.001). After cessation of exercise, i.e. during early recovery, SBP dropped by 17%, HR by 18%, and RPP by 43% (all P < 0.001 vs. exercise), although SBP, HR, and RPP remained significantly higher than resting values (P < 0.001).

**MBF, CFR, and coronary resistance**
The resting mean MBF value was 0.95 ± 0.20 mL/min/g. Bicycle exercise induced a significant increase in mean MBF to 2.52 ± 0.52 mL/min/g (168%, P < 0.001; Figure 1). MBF decreased by only 24% to 1.93 ± 0.50 mL/min/g during recovery measurement (P < 0.001), thus exerting a less pronounced drop compared with RPP (Figure 2).

CFR during exercise was 2.68 ± 0.51 and dropped by 24% to 2.03 ± 0.42 (P < 0.001) after cessation of exercise.

Coronary resistance dropped significantly during bicycle exercise compared with resting conditions (89 ± 15 vs. 40 ± 11 mmHg/mL/min/g, P < 0.001), but remained unchanged during recovery compared with bicycle exercise (40 ± 11 vs. 42 ± 9 mmHg/mL/min/g, P = ns; Figure 3).

All PET measurements are summarized in Table 2.
Discussion

The results of the present study show a discrepancy between decreased cardiac workload (as reflected by a declining RPP) and prolonged hyperaemic response during recovery after exercise. Interestingly, coronary resistance remains low during recovery after having significantly dropped during physical exercise. MBF is regulated by a complex interaction between vasodilator and vasoconstrictor mechanisms, exerted by the myocardium, endothelium, and neurohumoral systems; however, elevated myocardial oxygen consumption seems to be the major determinant of the elevated oxygen supply during exercise,2,21 while an increase in oxygen extraction is impossible as the latter is sealed in humans. Thus, it is a widely accepted fact that MBF in humans is linearly related to cardiac work.22–24 Most of this knowledge is based on the observation that an increase in cardiac work is accompanied by a proportional increase in MBF.2,22,24–28 Concordantly, in the present study, the increase in RPP at exercise was paralleled by a similar increase in MBF. Conversely, only sparse data exist on a possible correlation of MBF with the decreasing RPP during recovery. Recently, a decrease in RPP induced by pharmacological intervention with beta-receptor antagonists has been shown to cause a decrease in MBF in humans at rest,10 during physical exercise,25 or pharmacological stress.29

However, no data are available on the relation between myocardial work and blood flow during recovery after physical exercise in humans. Our results revealed that, during recovery, the close relation between RPP and MBF, which is typical during exercise, is no longer found. This surprising mismatch between a prolonged hyperaemic response and the rapid decline in RPP suggests an uncoupling of the close supply-demand mechanism, which generally determines the regulation of MBF. This is emphasized by the fact that coronary resistance significantly decreases during exercise and does not return immediately to baseline, but remains low during the early phase of recovery. Thus, despite decreasing oxygen consumption, the microcirculation preserves a high flow condition even after cessation of exercise. As we studied young healthy volunteers with negligible probability for coronary artery disease, it is unlikely that the prolonged hyperaemic response reflects a persistently high demand exceeding the actual consumption due to a preceding ischaemia during heavy exercise. Nevertheless, our results indicate that the association between workload and coronary resistance does not follow the same characteristic at recovery as it does during exercise, resulting in a loop rather than a linearity (Figure 3). This may, at least in part, be explained by the suggested mechanism of persistently high concentration of plasma catecholamines in the early post-exercise

Table 1 Haemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>Recovery</th>
<th>Delta Recovery (%)</th>
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</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>114 ± 11</td>
<td>145 ± 11*</td>
<td>125 ± 16*</td>
<td>-17 ± 9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>65 ± 9</td>
<td>72 ± 14†</td>
<td>61 ± 8†</td>
<td>-17 ± 16</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>81 ± 8</td>
<td>96 ± 10*</td>
<td>82 ± 9†</td>
<td>-18 ± 7</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>65 ± 12</td>
<td>133 ± 14*</td>
<td>92 ± 17†</td>
<td>-31 ± 9</td>
</tr>
<tr>
<td>RPP (bpm × mmHg)</td>
<td>7424 ± 1928</td>
<td>18 768 ± 1337*</td>
<td>11 652 ± 3224*†</td>
<td>-43 ± 13</td>
</tr>
</tbody>
</table>

Delta recovery, change in hyperaemic value during recovery compared with exercise; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; RPP, heart rate–blood pressure product (HR × SBP).

*P < 0.001 for comparison vs. rest.
†P < 0.05 for comparison vs. rest.
‡P < 0.01 for comparison vs. exercise.
period, raising myocardial oxygen demand by increasing myocardial contractility, even as rate pressure product decreases. In addition, sympathetic efferences have been shown to include coronary vasodilator effects in the absence of endothelial dysfunction and coronary artery disease. Finally, flow-mediated release of nitric oxide may persist for some time after exercise and contribute to the low resistance during recovery, an effect that is known to be disturbed in patients with coronary artery disease.

Our findings are in line with previously reported studies investigating blood flow and oxygen consumption during recovery in skeletal muscle. Although oxygen consumption remains elevated during recovery compared with resting conditions (a phenomenon known as excessive post-exercise oxygen consumption), a rapid decline during early recovery is found. Blood flow does not follow the same rapid decrease, leading to a similar mismatch between time course of blood flow and oxygen uptake in skeletal muscle. Although the exact mechanisms responsible for elevated blood flow in the first phase of recovery are still unclear, they seem to be associated with locally released vasodilator substances, such as adenosine, nitric oxide, and prostaglandins.

Overall, the loop between coronary resistance and exercise appears to characterize the dynamic ability of the microcirculation to comply with changing conditions of oxygen demand and supply. This microcirculatory compliance may be affected in patients with endothelial dysfunction and/or atherosclerosis, contributing to ischaemic reaction. This, however, was beyond the scope of the present study.

**Study limitations**

It may be perceived as a potential limitation of the present study that MBF was measured during recovery, representing a non-steady-state condition, while the method is based on the assumption of steady-state flow. However, we have previously established the repeatability of this method, documenting its reliability. In addition, the key results of the present study suggest that MBF was preserved during the early recovery—comparable to observations in skeletal muscles—and declined slowly enough to represent a steady state for the measurement.

Another limitation of this study is that individuals did not exercise at their maximal predicted level of effort. However, this was because exercise workload in the supine position usually accounts for only ~70% of the workload achieved in the upright position and individuals had to maintain workload constant over a time period of ~11 min.

Furthermore, motion artefacts may potentially affect image quality and data validity. We have, however, adjusted and fastened the volunteers to cycle ergometer with board straps over the upper body and fixed the patients’ shoulders as previously reported. In addition, confining the workload as mentioned above may have contributed to avoid motion artefacts. This was supported by excellent image quality and time–activity curves.

Finally, assessing myocardial oxygen consumption by acquiring LV pressure–volume loops may seem preferable. However, the chosen study setting (supine body position within the PET scanner) did not allow to adequately measure stroke volume by echocardiography. Despite being the most widely used non-invasive substitute in clinical routine, RPP is based on a simplified parameterization of the myocardial metabolism and therefore accounts for a notable limitation.
Conclusions
During early recovery immediately after cessation of physical exercise, there appears to be a mismatch between a rapid decrease in cardiac workload but preserved hyperaemic response. This suggests an uncoupling of low cardiac work and a persistently high MFB demand. Further studies are needed to elucidate whether this finding could potentially contribute to explain why early recovery may be susceptible to ischaemic ST-segment changes in coronary artery disease.

Conflict of interest: none declared.

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References