Effect of cardiac rehabilitation on angiogenic cytokines in postinfarction patients

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ABSTRACT
Objective: To determine whether cardiac rehabilitation influences plasma levels of angiogenic cytokines and their correlation with myocardial blood flow (MBF).

Design: Randomised controlled study.

Setting: Tertiary cardiac centre.

Patients: 39 postinfarction patients randomised to either a 3-month training group (n = 20) or a non-training group (n = 19), and 19 normal controls.

Interventions: Cardiac rehabilitation.

Main outcome measures: MBF by cardiac magnetic resonance imaging, and plasma levels of stem cell factor (SCF), stromal-derived factor-1 (SDF-1), and vascular endothelial growth factor (VEGF) measured at enrolment and at 3 months after randomisation.

Results: At baseline, when compared with the healthy subjects, postinfarction patients had a lower MBF in the infarcted myocardium during dipyridamole-induced stress (1.65 (0.58) vs 2.77 (0.78) ml/min/g, p = 0.001) but higher plasma levels of VEGF (3.65 (0.75) vs 2.77 (0.59) pg/ml, p = 0.01) than normal controls. After 3 months, the training group’s stress MBF had increased by 33% in the remote (r = −0.39, p = 0.03) and infarcted myocardium (r = −0.62, p = 0.001). Infarct-related artery with residual stenosis > 30% had undergone successful percutaneous coronary intervention with stent implantation of the infarct-related artery with residual stenosis > 30%.

Conclusion: Cardiac rehabilitation improves stress MBF in postinfarction patients, with an inverse decrease in circulating angiogenic cytokines.

Cardiac rehabilitation reduces coronary event rate and increases exercise capacity1–3 in patients with a prior myocardial infarction (MI). For such patients, a lack of perfusion at the microvascular levels is related to worse prognosis.4 Therefore, improved myocardial perfusion to the heart muscle would be a highly desirable outcome of cardiac rehabilitation. In fact, we have shown that improvements in exercise capacity are accompanied by increased myocardial perfusion reserve after exercise training.2 A deeper question is whether these clinical benefits are associated with angiogenic cytokines.

Angiogenic cytokines such as vascular endothelial growth factor (VEGF), stromal-derived factor-1 (SDF-1) and stem cell factor (SCF) are known to increase the formation of new vessels at ischaemic sites and thus enhance myocardial perfusion. Their levels in peripheral blood increase in response to endothelial damage,5 vascular trauma,6 acute MI8 and heart failure.9 On the other hand, chronic exercise does not raise plasma cytokine levels; rather, there appears to be a trend towards lowering them.10 Collectively, these studies suggest that angiogenic cytokines play a role in the training-induced improvement of myocardial perfusion. A better understanding of the role of surrogate markers of angiogenesis in chronic myocardial infarction and cardiac rehabilitation will provide clues to understanding the bigger issue of selecting patients for training in general. In this study, we investigated whether cardiac rehabilitation influences plasma levels of angiogenic cytokines in postinfarction patients. The secondary aim was to assess the relationship between plasma angiogenic cytokines and myocardial blood flow (MBF), especially in the infarcted myocardium.

METHODS
Study design
This prospective randomised controlled study was approved by the ethics committee of the National Taiwan University Hospital. The detailed study protocol and myocardial perfusion reserve results of the study have been reported previously.6 In brief, male patients ≤ 65 years old were eligible if they were admitted within 12 h after the onset of symptoms from a first ST-segment elevation MI, had undergone successful percutaneous coronary intervention with stent implantation of the infarct-related artery with residual stenosis < 50% of the vessel diameter, demonstrated a clinically stable course for at least 3 months after discharge, and showed no evidence of myocardial ischaemia on initial and follow-up exercise testing. The exclusion criteria were effort angina, atrial fibrillation, sustained ventricular arrhythmia, New York Heart Association functional class IV symptoms, exercise-limiting diseases, severe pulmonary or renal disease, an implanted pacemaker or claustrophobia.

Eligible patients who provided written informed consent were randomly assigned to the training group, which underwent a 3-month cardiac rehabilitation programme, or the non-training group in which patients continued their usual lifestyle. At baseline and the 3-month follow-up, all patients underwent a functional evaluation that included clinical evaluation, exercise testing, cardiac MRI and measurements of plasma angiogenic cytokines levels. Both groups were receiving stable and optimal pharmacological treatment supervised by their physicians. For comparison of myocardial
perfusion and angiogenic cytokines, age-, weight- and height-
matched subjects without cardiovascular risk factors were
selected as healthy controls. This study complies with the
Declaration of Helsinki.

Training protocol
The cardiac rehabilitation programme included health education
and exercise training. Exercise sessions were performed three
times a week for 12 weeks at 55% to 70% of the peak oxygen
uptake ($V_{O_2}$) measured in the initial exercise test and a
perceived exertion rating of 12 to 15 (fairly light to somewhat
hard) on the Borg scale. Each session consisted of a 5 min
warm-up period, a 20 min bicycle-ergometer exercise, and a
5 min cool-down period. The exercise session was supervised by
a physical therapist, and heart rate and blood pressure were
monitored during exercise. Patients in the non-training group
received educational support and continued their medications
but had no exercise training during the study period.

Exercise testing
Symptom-limited graded exercise testing was conducted with a
cycle ergometer (Ergotests; Erich Jaeger, Würzburg, Germany). Continuous electrocardiographic monitoring and analysis of
expired gases were performed during exercise testing. The
workload was 10 W for the first 3 min to make subjects familiar
with the exercise equipment and exercise techniques, and
thereafter the workload was increased by 10 W every minute.
The pedalling cadence was maintained between 50 and 70 rpm.
Breath-by-breath analysis of expired gas was performed using an
automated system (System 2000, Medical Graphics Corporation, St Paul, Minnesota). The mean value of peak
$V_{O_2}$ was determined from the final 20 s of the test and was expressed in ml/kg/min.

Cardiac MRI
All patients were examined in a 3-Tesla MRI scanner (Trio;
Siemens, Erlangen, Germany), and balanced steady-state free
precession cine images were acquired in two long-axis and seven
to nine short-axis views. After cine imaging was complete, an
intravenous bolus dose of 0.025 mmol/kg gadodiamide was
administered at a flow rate of 4 ml/s. First-pass perfusion
imaging was acquired with contrast injection, using an
electrocardiogram-gated non-slice-selective 90° saturation-
recovery preparation turbo fast low-angle shot pulse sequence.
The acquisition lasted for 80 heart beats, yielding 80 time
frames for each level at a temporal resolution of one R-to-R
interval. Perfusion studies were performed at rest and during the
stress induced by a 4 min infusion of dipyridamole at a
saturations were expressed as a percentage of LV mass. Results of perfusion studies and late
enhancement were analysed using the Mathematica software
package (Wolfram Research, Champaign, Illinois). The intraob-
server variability in the perfusion results was 6% and 5% in the
LV volume results.

Measurements of angiogenic cytokines
To rule out any effect of short-term exercise on cytokines
levels, blood samples were always taken after at least 72 h of
physical inactivity and overnight fasting when the subject had
rested in the sitting position for at least 10 min. The plasma
samples were immediately frozen and stored at −70°C. High-
sensitivity enzyme-linked immunosorbent assay kits (Bender
MedSystems, R&D) were used to measure plasma levels of SCF,
SDF-1 and VEGF according to the manufacturer’s protocols.
SDF-1 levels were assayed in platelet-depleted plasma samples
(centrifuged at 11 000 g for 10 min at 4°C). Each assay was
replicated twice, and a mean value was reported. In 19 age- and
sex-matched healthy volunteers, there were no significant
interval differences in angiogenic cytokines over a 3-month
period. The values at baseline and at the 3-month follow-up for
SCF levels were 524 (193) pg/ml and 506 (194) pg/ml, for SDF-1
levels were 1869 (309) pg/ml and 1812 (306) pg/ml and for the
log-transformed values of VEGF levels 2.77 (0.59) pg/ml and
2.66 (0.49) pg/ml, respectively. Intra-assay and interassay
variances were <5%.

Statistical analysis
Primary endpoint was the change from baseline in stress MBF in the
infarcted myocardium at 3 months’ follow-up. We calculat-
ed that we would need 18 patients in each group to achieve a
power of at least 80% to detect a 20% difference in MBF change
between study groups, with a two-sided significance level of
p<0.05, and a 20% increase for the stress MBF change from
baseline to 3 months' follow-up. All data are presented as the
mean (SD) for continuous data and as proportions for binary
data. If the data were not distributed normally, natural
logarithmic transformation would be used for analysis. Baseline
characteristics were compared using an unpaired Student t test for continuous data and $\chi^2$ analysis for binary
data. We used analyses of covariance to compare MBF changes in the two study groups with training treatment as the main
factor and MBF at baseline as a covariate. To estimate the
testing effect, differences in least-squares means and corre-
sponding 95% CI were calculated based on the model of
analyses of covariance. The consistency of the training effect on
MBF change was assessed across preliminary defined subgroups
of angiogenic cytokines. Median values of the patient popula-
tion were used to create subgroups of equal size. The correlations between angiogenic cytokines and clinical and

MRI measures were assessed with the Pearson correlation coefficient. All statistical tests were two-sided with a significance level of $p<0.05$. Statistical analyses were performed using the software package SPSS version 12.02 (SPSS, Chicago).

RESULTS

Clinical characteristics

Between August 2004 and December 2005, 91 patients were informed about the trial. Thirty-seven refused to participate, and 15 did not meet the inclusion criteria. The remaining 39 patients were enrolled in the study and randomised to either the training group ($n = 20$) or the non-training group ($n = 19$). Nineteen subjects without cardiovascular risk factors that were matched by age, weight and height were selected as healthy controls. Table 1 shows the comparison of demographic data between the 39 post-MI patients and 19 healthy subjects.

Compared with the healthy subjects (table 1), peak VO$_2$ and stress MBF in the infarcted myocardium were lower (both $p<0.01$), while plasma levels of SDF-1 and VEGF were higher in the post-MI patients (both $p<0.01$). However, there were no significant differences between the patients’ data and the healthy subjects’ reference values with respect to resting MBF in the infarcted myocardium, resting or stress MBF in the remote myocardium, and plasma SCF level.

The mean time from the onset of MI to initial evaluation was 8.3 (3.4) months (table 1). In about 60% of MI patients, the infarct-related artery was the left anterior descending artery. No significant differences between the training and non-training groups were observed in terms of age, cardiac structures and functions, infarct size, duration after MI or risk factors. The groups did not differ in medication taken. All patients maintained their own drug plan throughout the study. No patients died, were hospitalised for coronary intervention or had worsening symptoms during the 3-month study period.

Effects of cardiac rehabilitation on myocardial blood flow

Compared with the non-training group (table 2), patients in the training group had increased stress MBF in the remote myocardium (+33%, $p<0.001$) and infarcted myocardium (+28%, $p=0.02$) at 3 months. The effects of cardiac rehabilitation on the change in stress MBF in the infarcted myocardium at the 3-month follow-up were consistent among all investigated subgroups (fig 2). Besides, patients with higher cytokine levels before training showed a greater MBF improvement. In contrast, resting MBF was not affected by cardiac rehabilitation. No significant differences in MBF between baseline and follow-up levels were seen in the non-training group.

Effects of cardiac rehabilitation on angiogenic cytokines

Compared with the non-training group, patients in the training group had decreased VEGF ($-9\%$, $p=0.01$) and SDF-1 ($-11\%$, $p=0.02$) at 3 months (table 2). In contrast, the plasma SCF level was not significantly affected by cardiac rehabilitation. No significant differences in plasma angiogenic cytokines between baseline and follow-up levels were seen in the non-training group.

Clinical and cardiac MRI measures and angiogenic cytokines

At baseline, significant associations were found among SDF-1, exercise capacity and MBF (table 3). Plasma SDF-1 was significantly inversely associated with peak VO$_2$ ($r = -0.45$, $p<0.01$), resting MBF in the infarcted myocardium ($r = -0.32$, $p = 0.04$) and stress MBF in the remote ($r = -0.39$, $p = 0.03$) and infarcted myocardium ($r = -0.62$, $p<0.001$). A positive correlation was also found between SDF-1 and VEGF levels ($r = 0.33$, $p = 0.02$). In contrast, neither VEGF nor SCF was found to be associated with exercise capacity or MBF. Plasma levels of angiogenic cytokines were not associated with age, body surface area, cardiac contractility and infarct size.
Table 1 Baseline characteristics between the postinfarction patients and the healthy subjects at entry into the study

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n = 19)</th>
<th>Postinfarction patients (n = 39)</th>
<th>p Value (healthy controls vs all postinfarction patients)</th>
<th>p Value (non-training group vs training group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50 (36 to 62)</td>
<td>52 (39 to 65)</td>
<td>0.25</td>
<td>0.99</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.76 (0.13)</td>
<td>1.80 (0.13)</td>
<td>0.16</td>
<td>0.81</td>
</tr>
<tr>
<td>Peak oxygen uptake (ml/kg/min)</td>
<td>26.3 (4.4)</td>
<td>22.7 (3.1)</td>
<td>0.002</td>
<td>0.66</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>74 (6)</td>
<td>62 (13)</td>
<td>&lt;0.001</td>
<td>0.33</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>3.1 (0.4)</td>
<td>3.0 (0.6)</td>
<td>0.99</td>
<td>0.58</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>58 (17)</td>
<td>75 (14)</td>
<td>0.001</td>
<td>0.42</td>
</tr>
<tr>
<td>Blood flow in remote myocardium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest (ml/min/g)</td>
<td>1.15 (0.24)</td>
<td>1.07 (0.18)</td>
<td>0.13</td>
<td>0.50</td>
</tr>
<tr>
<td>At stress (ml/min/g)</td>
<td>2.77 (0.78)</td>
<td>2.59 (0.64)</td>
<td>0.17</td>
<td>0.35</td>
</tr>
<tr>
<td>Blood flow in infarcted myocardium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest (ml/min/g)</td>
<td>1.15 (0.24)</td>
<td>1.07 (0.37)</td>
<td>0.14</td>
<td>0.20</td>
</tr>
<tr>
<td>At stress (ml/min/g)</td>
<td>2.77 (0.78)</td>
<td>1.70 (0.52)</td>
<td>&lt;0.001</td>
<td>0.64</td>
</tr>
<tr>
<td>Stromal-derived factor-1 (pg/ml)</td>
<td>1869 (309)</td>
<td>2104 (309)</td>
<td>0.009</td>
<td>0.89</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (pg/ml)</td>
<td>2.77 (0.59)</td>
<td>3.46 (0.61)</td>
<td>&lt;0.001</td>
<td>0.69</td>
</tr>
<tr>
<td>Stem cell factor (pg/ml)</td>
<td>524 (183)</td>
<td>568 (85)</td>
<td>0.15</td>
<td>0.18</td>
</tr>
<tr>
<td>Left anterior descending artery as infarct-related artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postinfarction period (months)</td>
<td>7.9 (3.5)</td>
<td>8.6 (3.3)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>8 (42%)</td>
<td>&lt;0.001</td>
<td>0.88</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>3 (16%)</td>
<td>0.12</td>
<td>0.83</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>0</td>
<td>8 (42%)</td>
<td>&lt;0.001</td>
<td>0.63</td>
</tr>
<tr>
<td>Remote smokers</td>
<td>0</td>
<td>7 (37%)</td>
<td>0.003</td>
<td>0.62</td>
</tr>
<tr>
<td>Active smokers</td>
<td>0</td>
<td>0</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors or</td>
<td>0</td>
<td>11 (58%)</td>
<td>&lt;0.001</td>
<td>0.63</td>
</tr>
<tr>
<td>Angiotensin II type 1 receptor blockers use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker use</td>
<td>0</td>
<td>15 (78%)</td>
<td>&lt;0.001</td>
<td>0.86</td>
</tr>
<tr>
<td>Statin use</td>
<td>0</td>
<td>8 (42%)</td>
<td>&lt;0.001</td>
<td>0.63</td>
</tr>
</tbody>
</table>

*The reference values of blood flow in infarcted myocardium are the same as those in remote myocardium in healthy controls. All values are expressed as mean (SD) or the number (%) of patients except age expressed as median and range. The value of vascular endothelial growth factor has been logarithmically transformed. Hypertension is defined as a repeatedly elevated blood pressure >140/90 mm Hg or current use of antihypertensive medication. Hyperlipidaemia is defined as fasting total cholesterol >5.27 mmol/l, low-density lipoprotein (LDL) cholesterol >3.42 mmol/l, triglyceride >2.27 mmol/l or current use of lipid-lowering drugs.

LV, left ventricular.

Figure 2 Subgroup analyses of changes in stress myocardial blood flow (MBF) in the infarcted myocardium from baseline at 3-month follow-up. *Median values of the patient population were used to create subgroups of equal size. Oval dots show differences in least-squares means between groups; horizontal bars show the 95% confidence interval. SDF, stromal-derived factor-1; VEGF, vascular endothelial growth factor.
Cardiac rehabilitation

After 3 months, the percentage change in plasma levels of SDF-1 was inversely correlated not only with the change in peak VO₂ (r = –0.38, p = 0.02) but also with the change in stress MBF in the remote myocardium (r = –0.40, p = 0.01; fig S) and infarcted myocardium (r = –0.50, p = 0.001; fig 3). The percentage change in VEGF was inversely correlated with the change in peak VO₂ (r = –0.40, p<0.01). However, there was no association between the percentage change in VEGF and the change in MBF, at rest or at stress, in the remote or infarcted myocardium. There was no association between the percentage change in SCF and the change in MBF or exercise capacity.

DISCUSSION

The present study investigates the effect of cardiac rehabilitation on angiogenic cytokines and their relationships with absolute MBF in the postinfarction patients, where there are three main findings. First, we report that in the late postinfarction period, higher plasma levels of angiogenic cytokines exist with a lower value of stress MBF in infarcted myocardium. Among the angiogenic cytokines measured in this study, only SDF-1 was significantly inversely associated with stress MBF, especially in the infarcted myocardium. Second, we show that cardiac rehabilitation reduces the cytokines levels and concordantly improves stress MBF in the whole myocardium. Finally, we demonstrate that a reduction in plasma SDF-1 is associated with an increase in stress MBF, especially in the infarcted myocardium. Thus, for the first time, this study has identified SDF-1 as a molecular marker that may reflect stress perfusion that may reflect the outcome after cardiac rehabilitation.

To the best of our knowledge, the present study is the first study to concurrently examine the relationship between angiogenic cytokines and myocardial perfusion serially with a validated quantitative MRI technique over the course of cardiac rehabilitation. In our previous report, an increase in stress perfusion index in the infarcted myocardium after cardiac rehabilitation was considered to be the result of the functional recovery of resistant vessels because other major contributors

Table 2  Exercise capacity, cardiac MRI measures and angiogenic cytokines at baseline and 3-month follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-training</td>
<td>Training</td>
<td>Non-training</td>
</tr>
<tr>
<td>Peak oxygen uptake (ml/kg/min)</td>
<td>22.7 (3.1)</td>
<td>22.2 (3.9)</td>
<td>22.4 (3.0)</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>62 (13)</td>
<td>58 (12)</td>
<td>62 (12)</td>
</tr>
<tr>
<td>Cardiac index, l/min/m²</td>
<td>3.0 (0.6)</td>
<td>3.1 (0.5)</td>
<td>3.0 (0.6)</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>75 (14)</td>
<td>79 (16)</td>
<td>77 (15)</td>
</tr>
<tr>
<td>Infarct size, g</td>
<td>22 (11)</td>
<td>29 (15)</td>
<td>22 (11)</td>
</tr>
</tbody>
</table>

Perfusion in infarcted myocardium

Rest (ml/min/g) | 1.07 (0.18) | 1.03 (0.19) | 1.07 (0.14) | 1.21 (0.26) | 0.00 (0.22) | 0.18 (0.31) | 0.05 (−0.10 to 0.20) | 0.49 |
Stress (ml/min/g) | 2.59 (0.64) | 2.36 (0.87) | 2.32 (0.48) | 2.98 (0.90) | −0.27 (0.56) | 0.62 (0.83) | 0.79 (0.38 to 1.20) <0.001 |

Perfusion in remote myocardium

Rest (ml/min/g) | 1.07 (0.37) | 0.92 (0.34) | 0.89 (0.22) | 0.94 (0.27) | −0.18 (0.46) | 0.02 (0.41) | 0.05 (−0.12 to 0.21) | 0.58 |
Stress (ml/min/g) | 1.70 (0.52) | 1.61 (0.65) | 1.70 (0.52) | 2.05 (0.83) | 0.00 (0.46) | 0.44 (0.71) | 0.45 (0.07 to 0.83) | 0.02 |
Stromal-derived factor-1 (pg/ml) | 2104 (309) | 2118 (344) | 2070 (311) | 1876 (343) | −68 (175) | −196 (209) | −131 (−246 to −16) | 0.02 |
Vascular endothelial growth factor (pg/ml) | 3.46 (0.61) | 3.54 (0.62) | 3.51 (0.59) | 3.22 (0.63) | −0.05 (0.38) | −0.35 (0.35) | −0.31 (−0.52 to −0.08) | 0.01 |
Stem cell factor (pg/ml) | 568 (85) | 625 (163) | 585 (60) | 645 (164) | 17 (47) | 20 (120) | 20 (−37 to 76) | 0.49 |

Training effects expressed as differences in least-squares means (model of analyses of covariance) with 95% CI. The value of vascular endothelial growth factor has been logarithmically transformed.

LV, left ventricular.

Table 3  Correlation between the plasma levels of angiogenic cytokines and clinical and cardiac MRI measures in 39 postinfarction patients

<table>
<thead>
<tr>
<th></th>
<th>Stem cell factor (pg/ml)</th>
<th>Stromal-derived factor-1 (pg/ml)</th>
<th>Vascular endothelial growth factor (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>r = 0.17</td>
<td>r = −0.16</td>
<td>r = −0.19</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>r = −0.16</td>
<td>r = 0.33</td>
<td>r = 0.22</td>
</tr>
<tr>
<td>Peak oxygen uptake (ml/kg/min)</td>
<td>r = −0.09</td>
<td>r = 0.57</td>
<td>r = −0.45</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>r = −0.08</td>
<td>r = 0.63</td>
<td>r = 0.07</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>r = 0.05</td>
<td>r = 0.75</td>
<td>r = −0.22</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>r = −0.22</td>
<td>r = 0.18</td>
<td>r = −0.03</td>
</tr>
<tr>
<td>Infarct size (g)</td>
<td>r = 0.01</td>
<td>r = 0.93</td>
<td>r = −0.15</td>
</tr>
<tr>
<td>Blood flow in remote myocardium at rest (ml/min/g)</td>
<td>r = −0.20</td>
<td>r = 0.23</td>
<td>r = −0.28</td>
</tr>
<tr>
<td>Blood flow in remote myocardium at stress (ml/min/g)</td>
<td>r = 0.05</td>
<td>r = 0.78</td>
<td>r = −0.39</td>
</tr>
<tr>
<td>Blood flow in infarcted myocardium at rest (ml/min/g)</td>
<td>r = 0.07</td>
<td>r = 0.70</td>
<td>r = −0.32</td>
</tr>
<tr>
<td>Blood flow in infarcted myocardium at stress (ml/min/g)</td>
<td>r = 0.05</td>
<td>r = 0.77</td>
<td>r = −0.62</td>
</tr>
</tbody>
</table>

The value of vascular endothelial growth factor has been logarithmically transformed.

LV, left ventricular.
and SDF-1 are known to play a significant role in the elevation of plasma VEGF and SDF-1 than healthy subjects. Both VEGF and SDF-1 qualify as one of the major research targets.

vasculogenesis and blood-vessel development and, as such, are possible directions of research, an angiogenic cytokine, such as VEGF, ischaemia is known to stimulate an elevation in myocardial and plasma levels of VEGF and SDF-1. In the present study, we showed an inverse relationship between SDF-1 levels and MBF in post-MI patients, suggesting that a high plasma level of SDF-1 might be a marker of myocardial hypoperfusion. Beyond being atherosclerotic contributors and angiogenic cytokines, both SDF-1 and VEGF are chemokines that are involved in the recruitment of stem cells or endothelial progenitor cells to the injured organ. In fact, upregulation of SDF-1 in the injured myocardium, and consequently in the circulation, is a prerequisite first step in initiating mobilisation and recruitment of stem cells to the injured heart. Taken together, it is tempting to speculate that higher plasma levels of angiogenic cytokines after MI may represent a plaque burden in pre-existing coronary artery disease or may signal an ischaemic myocardium, which increases demand for stem-cell mobilisation to the heart for neovascularisation or repair.

Another cytokine, SCF, is known to interact synergistically with VEGF to mobilize stem cells and improve chronic myocardial ischaemia in an animal study. Although no relation with MBF was observed in this study, post-MI patients tended to have higher plasma SCF levels. Since we used the plasma of venous samples to measure the concentration of cytokines, and since this type of plasma is subject to the influence of washout dilution from ischaemic tissue to systemic circulation, the relationship might not necessarily be demonstrated.

Acute bouts of exercise or ischaemic exercise training may raise plasma levels of angiogenic cytokines. However, in the resting steady-state condition, there appears to be a trend towards lower circulating angiogenic cytokine levels after subischaemic exercise training, a finding confirmed in the present trial. The present study shows that cardiac rehabilitation decreases plasma levels of VEGF and SDF-1, and that the extent of their diminution is related to the increase in stress MBF and exercise capacity. Following the discussion above, the influence of cardiac rehabilitation on the angiogenic cytokines could be attributed to improved myocardial perfusion by the regression of coronary atherosclerosis or the augmentation of vascular bed. Few data address whether exercise slows progression of atherosclerotic plaque. A 6-year randomised, controlled trial demonstrates that regular physical exercise at low to moderate intensity can attenuate progression of carotid atherosclerosis in men, but the effect is not seen until the 3-year exercise. Thus, the former viewpoint is less likely to be true in this 3-month rehabilitation programme. The latter viewpoint is supported by several recent reports that short-term exercise training induced mobilisation of endothelial progenitor cells from bone marrow to peripheral blood and thereby may improve endothelial regeneration and collateral formation into ischaemic myocardium. The present study demonstrates that a reduction in plasma SDF-1 in the training group correlates with an increase in stress MBF, suggesting a feedback regulation of SDF-1 due to increased blood supply to the myocardium after cardiac rehabilitation. Thus, a serial assay of plasma SDF-1 levels appears to be a valuable method to evaluate the clinical outcome of cardiac rehabilitation.
Study limitations
Several study limitations should be considered when interpreting these findings. First, in view of the small size of our trial, our findings must be considered with caution. Even though this was a prospective randomised controlled study, our results need to be confirmed in a larger cohort. With this limitation in mind, it is noteworthy that the patient number in each group was larger than the predetermined sample size by power analysis. Second, these results are applicable only for male patients < 65 years old with ST-segment elevation MI after successful percutaneous coronary intervention. Further studies should also be performed on female patients. Third, the source of the measured plasma concentration of angiogenic cytokines cannot be elucidated. SDF-1 is produced in almost all organs, but most abundantly in the bone marrow and ischaemic organs. Although we demonstrate a moderate association between plasma SDF-1 and myocardial perfusion in the post-MI patients, Fig 3 demonstrates that the relationship does not appear to be linear. In this type of analysis where the number of data points is relatively small, and the relationship is not actually linear, the slope of the regression line can be heavily influenced by only a couple of data points. This observation further highlights the weak correlation between these variables. Further studies using blood samples from coronary sinususes and in a larger cohort may ascertain this relationship more firmly.

Conclusion
This study suggests that postinfarction patients with elevated SDF-1 levels are more likely to have clinical benefits after cardiac rehabilitation, but the study was too small to allow meaningful subgroup analyses. A large prospective study is needed to determine whether including serial measurements of SDF-1 during follow-up improves the ability to detect myocardial hypoperfusion and thereby allows early cardiac rehabilitation.

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