Reduced coronary and inotropic reserves with coronary microembolization

ANDREAS SKYSCHALLY,1 RAINER SCHULZ,1 RAIMUND ERBEL,2 AND GERD HEUSCH1

1Abteilungen für Pathophysiologie und 2Kardiologie, Zentrum für Innere Medizin,
Universitätsklinikum Essen, 45122 Essen, Germany

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Skyschally, Andreas, Rainer Schulz, Raimund Erbel, and Gerd Heusch. Reduced coronary and inotropic reserves with coronary microembolization. Am J Physiol Heart Circ Physiol 282: H611–H614, 2002. First published October 18, 2001; 10.1152/ajpheart.00797.2001.—Microembolized myocardium is characterized by perfusion-contraction mismatch with reduced contractile function and unchanged or even elevated blood flow. The present study investigated the consequences of microembolization on coronary and inotropic reserves. In eight anesthetized dogs, left circumflex coronary blood flow (CBF), regional blood flow (RBF), and posterior systolic wall thickening were measured. Repetitive injection of 42-μm microspheres into the left circumflex coronary artery decreased systolic wall thickening by 50% (17.2 ± 2.4% vs. 8.0 ± 1.4%; means ± SD). Coronary reserve was determined by either intracoronary infusion of adenosine (n = 4) or the reactive hyperemia response following 15 s of coronary occlusion (n = 4); inotropic reserve was recruited by intracoronary infusion of dobutamine. The amount of injected microspheres was 158,000 ± 48,000. CBF (45.5 ± 16.5 vs. 47.8 ± 14.4 ml/min) and RBF (1.15 ± 0.18 vs. 1.33 ± 0.39 ml·min⁻¹·g⁻¹) remained unchanged. Coronary reserve in response to intracoronary infusion of adenosine (410 ± 94% vs. 290 ± 77%; P < 0.05) and reactive hyperemia repayment (360 ± 174% vs. 155 ± 66%; P < 0.05) were blunted after microembolization. Inotropic reserve, i.e., the increment in systolic wall thickening with dobutamine, was decreased from 12.4 ± 3.9% to 8.0 ± 3.3% (P < 0.05). We conclude that coronary microembolization reduces coronary and inotropic reserves.

atherosclerosis; embolism; microcirculation; regional blood flow; regional myocardial function

ATHEROSCLEROTIC PLAQUE RUPTURE, occurring either spontaneously or during coronary interventions, results in the release of atheromatous and/or thrombotic material into the coronary circulation, which may embolize the microvascular bed (8,16). Experimental microembolization results in a perfusion-contraction mismatch, i.e., myocardial function is markedly reduced, whereas coronary blood flow remains unchanged or is even increased. Such an increase in coronary blood flow was attributed to vasodilation of adjacent nonembolized vessels in response to adenosine release from the microembolized myocardium (10,14). The loss of contractile function in microembolized myocardium was attributed to inflammatory processes, in particular tumor necrosis factor-α (6,7). Microembolization was also suggested in a recent clinical study where patients who had elevated serum creatine kinase and troponin T concentrations after a percutaneous coronary intervention, reflecting microinfarction, were also characterized by increased coronary blood flow at baseline and reduced coronary flow reserve (11). Inotropic reserve in microembolized myocardium has not been studied so far.

The present study now investigated the impact of controlled coronary microembolization on coronary and inotropic reserves in anesthetized dogs in vivo.

METHODS

The experimental protocols were approved by the bioethical committee of the district of Düsseldorf, Germany. The animals were handled according to the guidelines of the American Physiological Society.

Experimental preparation. Eight mongrel dogs (22–34 kg body wt) were anesthetized with an initial bolus of thiameylal sodium (15 mg/kg iv). After endotracheal intubation, anesthesia was maintained by ventilation with the use of enflurane with an oxygen-nitrous oxide mixture. Left ventricular and aortic pressures were measured with catheter-tipped manometers (PC 350, Millar; Houston, TX).

Heart rate and the first derivative of left ventricular pressure (dP/dt) were derived from the left ventricular pressure signal. A left thoracotomy was performed in the fifth intercostal space. The pericardium was opened and sutured to cradle the heart. Regional myocardial blood flow was measured using colored 15-μm microspheres (15). Ultrasonic crystals were implanted in the anterior left ventricular wall and in the posterolateral wall perfused by the left circumflex coronary artery (LCX) for measurement of regional myocardial wall thickness. The LCX was dissected free for ~2 cm proximal to its first branch. A 27-gauge needle was inserted into the LCX, distal to an electromagnetic flow probe, for intracoronary injection of embolizing microspheres or infusion of adenosine or dobutamine. A snare occluder was placed immediately distal to the 27-gauge needle.

Experimental protocol. After stabilization, measurements of systemic hemodynamics, regional myocardial blood flow,
and function at baseline were performed. Coronary reserve was recruited by either intracoronary infusion of adenosine \((n = 4; 160 \mu g/min)\) or the reactive hyperemia response following 15 s of coronary occlusion \((n = 4)\). The reactive hyperemia repayment was calculated as the percent ratio between the deficit of coronary inflow during occlusion and the integral of coronary blood flow above the preclosure flow (5). Inotropic reserve was recruited by intracoronary infusion of dobutamine at a dose that caused a maximal increase in regional systolic myocardial wall thickening \((n = 8; 5.6 \pm 3.7 \mu g/min)\); i.e., a higher dose did not further increase wall thickening.

Microembolization was induced by repetitive injection of 30,000 microspheres \((42-\mu m\) Dynospheres; Dyno Particles; Lillestrøm, Norway) into the LCX. After an immediate decrease after the injection, coronary blood flow and systolic wall thickening recovered and stabilized after a few minutes. The injection of 30,000 microspheres was repeated until systolic wall thickening of the posterior wall was reduced by \(~50\%\) of the control value (Fig. 1). Measurements of systemic hemodynamics, regional myocardial blood flow, and coronary and inotropic reserves were then repeated. The doses of adenosine or dobutamine were the same as under control conditions.

After the experiment the heart was removed, and samples from the posterior and anterior wall where regional myocardial function was measured were taken. Tissue digestion, extraction of the dye, and calculation of regional myocardial blood flow were performed as described previously (15).

**Statistics.** Statistical analysis was performed with the use of SYSTAT software \((Urbana, IL)\). Data are reported as mean values \(\pm SD\). Changes in hemodynamics and regional myocardial function were estimated by two-way ANOVA \((control vs. microembolization and baseline vs. adenosine or dobutamine)\), including an interaction term. When a significant overall effect was detected, least significant difference post hoc tests were performed to compare single mean values. Coronary and inotropic reserves and regional blood flow before and after microembolization were compared by paired \(t\)-tests. A \(P\) value \(<0.05\) indicated a significant difference.

**RESULTS**

**Hemodynamics, regional myocardial function, and blood flow at baseline.** Posterior systolic wall thickening was reduced to \(47\%\) of the control value by injection of 158,000 \(\pm\) 48,000 microspheres, i.e., 3,710 \(\pm\) 1,630 spheres ml\(^{-1}\)-min coronary blood flow\(^{-1}\). Coronary blood flow and regional myocardial blood flow in the posterior wall were slightly increased. Regional myocardial blood flow and function in the anterior wall remained unchanged. Systemic hemodynamics did not change with coronary microembolization (Table 1). The time from the first injection of embolizing spheres to measurements with established microembolization was 43 \(\pm\) 11 min; the time from the last microspheres injection to measurements was 12 \(\pm\) 6 min.

**Coronary reserve.** The intracoronary infusion of adenosine \((160 \mu g/min)\) increased mean coronary blood flow in the LCX before and after microembolization.

### Table 1. Systemic hemodynamic data

<table>
<thead>
<tr>
<th></th>
<th>HR, beats/min</th>
<th>LVP, mmHg</th>
<th>dP/dt(_{\text{min}}), mmHg/s</th>
<th>dP/dt(_{\max}), mmHg/s</th>
<th>PWT, %</th>
<th>AWT, %</th>
<th>CBF, ml/min</th>
<th>PW(_{\text{r}}), ml(\cdot)min(^{-1})g(^{-1})</th>
<th>AW(_{\text{r}}), ml(\cdot)min(^{-1})g(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con</td>
<td>127 (\pm) 9</td>
<td>107 (\pm) 10</td>
<td>(-2,016 \pm 213)</td>
<td>(1,538 \pm 141)</td>
<td>17.2 (\pm) 2.4</td>
<td>21.3 (\pm) 4.9</td>
<td>45.5 (\pm) 16.5</td>
<td>1.15 (\pm) 0.18</td>
<td>1.19 (\pm) 0.17</td>
</tr>
<tr>
<td>Con + Ado</td>
<td>131 (\pm) 2</td>
<td>109 (\pm) 9</td>
<td>(-1,971 \pm 133)</td>
<td>(1,560 \pm 228)</td>
<td>14.8 (\pm) 2.1</td>
<td>19.5 (\pm) 4.4</td>
<td>191.2 (\pm) 32.6</td>
<td>87.2 (\pm) 37.3</td>
<td></td>
</tr>
<tr>
<td>Con + Dob</td>
<td>131 (\pm) 13</td>
<td>110 (\pm) 12</td>
<td>(-2,128 \pm 404)</td>
<td>(1,964 \pm 210)</td>
<td>26.3 (\pm) 3.9</td>
<td>16.1 (\pm) 5.9</td>
<td>148.3 (\pm) 28.2</td>
<td>87.2 (\pm) 37.3</td>
<td></td>
</tr>
<tr>
<td>ME</td>
<td>123 (\pm) 10</td>
<td>104 (\pm) 11</td>
<td>(-1,731 \pm 193)</td>
<td>(1,348 \pm 117)</td>
<td>8.0 (\pm) 1.4</td>
<td>18.5 (\pm) 4.5</td>
<td>47.8 (\pm) 14.4</td>
<td>1.33 (\pm) 0.39</td>
<td>1.17 (\pm) 0.23</td>
</tr>
<tr>
<td>ME + Ado</td>
<td>125 (\pm) 5</td>
<td>111 (\pm) 5</td>
<td>(-1,795 \pm 95)</td>
<td>(1,403 \pm 107)</td>
<td>7.2 (\pm) 0.8</td>
<td>17.0 (\pm) 5.8</td>
<td>148.5 (\pm) 55.4</td>
<td>1.26 (\pm) 0.39</td>
<td>1.17 (\pm) 0.23</td>
</tr>
<tr>
<td>ME + Dob</td>
<td>132 (\pm) 13</td>
<td>111 (\pm) 13</td>
<td>(-1,958 \pm 396)</td>
<td>(1,925 \pm 176)</td>
<td>14.2 (\pm) 4.7</td>
<td>17.3 (\pm) 6.4</td>
<td>85.2 (\pm) 25.8</td>
<td></td>
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</tr>
</tbody>
</table>

Values are means \(\pm SD\). Con, control; ME, microembolization; Ado, intracoronary infusion of adenosine \((n = 4\) dogs); Dob, intracoronary infusion of dobutamine \((n = 8\) dogs); HR, heart rate; LVP, left ventricular peak pressure; dP/dt, first derivative of LVP; PW\(_{\text{r}}\) and AW\(_{\text{r}}\), regional myocardial blood flow in the posterior/anterior wall; CBF, mean coronary blood flow in left circumflex coronary artery; PW\(_{\text{r}}\) and AW\(_{\text{r}}\), regional myocardial blood flow in the posterior/anterior wall. *\(P < 0.05\) vs. Con; †\(P < 0.05\) vs. ME.
This increase, expressed as a percentage of baseline, was reduced (410 ± 94% vs. 290 ± 77%) following microembolization (Fig. 2). Systemic hemodynamics remained unchanged during adenosine infusion. The reactive hyperemia repayment following a 15-s occlusion of the LCX was reduced from 360 ± 174% to 155 ± 66% following microembolization (Fig. 2).

Inotropic reserve. The intracoronary infusion of dobutamine (5.6 ± 3.7 μg/min) increased left ventricular dP/dt and coronary inflow. After microembolization, the increment in systolic wall thickening of the posterior wall was reduced from 12.4 ± 3.9% to 8.0 ± 3.3% (Fig. 3).

DISCUSSION

The present study confirmed the existence of perfusion-contraction mismatch in microembolized myocardium (6) and further characterized microembolized myocardium by reduced coronary and inotropic reserves. Microembolized myocardium is a mixture of hypoperfused myocardium suffering from ischemia and microinfarction (6) and hyperperfused surrounding myocardium with vasodilation secondary to a release of adenosine (14). The net effect may be an unchanged or even increased blood flow at baseline, with reduced coronary flow reserve. This same pattern is also seen in patients undergoing a percutaneous coronary intervention who have increased baseline average peak velocity and reduced coronary flow velocity reserve. Serum creatine kinase and troponin T were increased in these patients, reflecting microinfarction (11). We assumed, therefore, that coronary microembolization had occurred in these patients. Our present experimental data support this assumption because controlled coronary microembolization indeed reduces coronary reserve. We did not see a difference in baseline regional contractile function and blood flow before and after coronary microembolization between dogs that had recruitment of coronary reserve by adenosine or by reactive hyperemia. Preconditioning against the consequences of coronary microembolization by exogenous adenosine, therefore, appears unlikely.

Microembolized myocardium is characterized by depressed myocardial function in the presence of normal or even elevated myocardial blood flow. The mechanical disadvantage is obviously related to both the number and size of embolizing microspheres. When a cardiac output of 3 l/min was assumed, the number of 15-μm microspheres for the measurement of myocardial blood flow was 160,000 and decreased regional systolic wall thickening by 9 ± 6% (NS), in contrast to 158,000 microspheres of 42 μm diameter, which decreased systolic wall thickening by 53 ± 6%. Phenomenologically, the same perfusion-contraction mismatch pattern as in coronary microembolization is seen in stunned myocardium (2, 12). An inotropic reserve is recruitable in both the microembolized and the stunned myocardium. Whereas the inotropic reserve is unaltered in stunned compared with normal myocardium by reduced coronary and inotropic reserves. Microembolized myocardium is a mixture of hypoperfused myocardium suffering from ischemia and microinfarction (6) and hyperperfused surrounding myocardium with vasodilation secondary to a release of adenosine (14).
dium (2), the inotropic reserve in the present study was blunted by \( \sim 25\% \) after microembolization. This decrease in the inotropic reserve can probably be attributed to patchy microinfarcts, which in a recent study from our laboratory that used embolizing particles of the same size and a comparable amount of 3,000 particles\( \cdot \)ml\(^{-1} \)\cdot min coronary blood flow\(^{-1} \) resulted in an aggregate infarct size of 6.5% of the area at risk (6). Apart from perfusion-contraction mismatch and a preserved inotropic reserve, microembolized and stunned myocardium are also mechanistically related, i.e., free oxyradicals are involved in the pathogenesis of both the microembolized and the stunned myocardium, and the respective contractile dysfunction is attenuated by destruction of free radicals by superoxide dismutase/catalase (1, 3, 9, 13). Thus stunned and microembolized myocardium are both characterized by regional contractile dysfunction in the presence of normal regional blood flow, persistent inotropic, and reduced coronary reserve (4). The reduction in inotropic reserve together with the plasma marker release, which reflects microinfarction, may help to quantify the extent of irreversible damage in patients.

We conclude that coronary microembolization reduces coronary and inotropic reserves. Our experimental data therefore support the notion that patients who have increased baseline flow and reduced coronary flow reserve after coronary interventions together with marker release that reflects microinfarction (11) may indeed have experienced microembolization.

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REFERENCES


