Relationship between surface area of nonperfused myocardium and extravascular extraction of contrast agent following coronary microembolization

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Microvascular permeability can change under various pathologic and metabolic circumstances such as diabetes mellitus (24, 41), hypercholesterolemia (32), hypertension (31), and acute myocardial ischemia followed by reperfusion (29). Embolization of microscopic plaque debris into the distal coronary bed during coronary interventions is a common and frequent event (9, 10, 35) that might be associated with microinfarctions and with adverse clinical outcome (7, 10).

We have previously demonstrated that experimental coronary microembolization leads to a decrease in regional myocardial contractility that is proportional to the surface area of the embolization-induced nonperfused islands (microperfusion defects) in the myocardium (23). However, the effect of this maneuver on microvascular integrity or the factors that determine the magnitude of the extravascular accumulation of contrast agent remained unknown.

The consequences of increased permeability to solutes can be observed only if there is, in fact, delivery to the microvasculature, i.e., in the presence of ongoing perfusion. Permeability affecting mediators originating from disintegrated tissue can more easily and likely diffuse from the interfacial region between perfused and nonperfused myocardium (i.e., short distance, proportional to the interface’s surface area) into the perfused myocardium and corresponding microvasculature rather than from deep within the nonperfused myocardium (long diffusion distance). Consequently, the movement of water and solutes from the intravascular into the extravascular compartment should primarily occur at the interface between the nonperfused and perfused territories. Based on these observations, we hypothesize that 1) coronary microembolization leads to an increase of microvascular permeability of the endothelium in the microvessels within the perfusion territory embolized, and 2) the increase in extravascular water and solutes due to the increased permeability is directly related to the total surface area of the interface between the nonperfused and surrounding perfused myocardium.

To test these hypotheses, we used two complementary imaging modalities. Electron beam computed tomography (EBCT) was used to obtain in vivo indices of myocardial perfusion (F, flow; ml·g myocardium⁻¹·min⁻¹), microvascular permeability (30), and intramyocardial blood volume as the surrogate for vascular surface area (Bv, blood volume; ml/g myocardium). After completion of the EBCT-based studies, an X-ray microcomputed tomography scanner (micro-CT) was used to obtain directly, ex vivo, the volume and the total surface area of the individual nonperfused, ischemic, myocardial territories within the same region of myocardium that was previously scanned by the EBCT. Micro-CT provides a unique tool for quantification of 3D vascular structures and the number, volume, and surface area of the individual myocardial perfusion defects in a relatively large volume (>1 cm³) of embolized myocardium (22, 23). For testing our hypotheses in an in situ heart in an animal model, we used anesthetized pigs.
because their coronary circulation closely resembles human heart anatomy, blood flow distribution, and function (37). Different sizes and doses of microspheres were used to explore the relationship between the surface area and increase in microvascular permeability over a wide range of individual-sized perfusion defects and to mimic the clinically observed heterogeneous nature in sizes and quantity of embolizing particle debris during coronary interventions (2). The aim of this study was therefore to quantify changes in coronary microvascular permeability to the nonionic contrast agent iopamidol following coronary microembolization with polymer microspheres in the perfusion territory of porcine left anterior descending coronary artery.

MATERIAL AND METHODS

Animal preparation. The study protocol was approved by the Mayo Foundation Institutional Animal Care and Use Committee. Thirty-four domestic, crossbred (all female, mean weight: 32.0 ± 3 kg), 3 mo old pigs were initially anesthetized and instrumented as described previously (21, 27). Briefly, the left internal jugular vein and the left carotid artery were exposed via cut down. Sheaths were placed in the left carotid artery (8 French) and in the left jugular vein (7 French), respectively. Under fluoroscopic guidance, a left coronary guide catheter was placed in the left main coronary artery for coronary angiography and monitoring proximal coronary artery pressure. The tip of a 2.2-French, dual-lumen, infusion catheter was advanced via the 8 French catheter, and its tip placed in the proximal left anterior descending coronary artery (LAD) between the second and third diagonal branches for selective intracoronary infusion of adenosine and microspheres.

EBCT studies. To overcome the cardiogenic motion imaging artifacts, we used EBCT, a fast CT with a single-scan acquisition time of 50 ms, which could be repeated 17 times per second. This scanner has been proven to be an accurate (4), reproducible (25), and minimally invasive (27) tool for in vivo study of microcirculatory functional parameters, such as myocardial perfusion and permeability indices (27, 29, 30, 32). The technical properties of the EBCT scanner (model C-150; Imatron, South San Francisco, CA) have been described in detail elsewhere (27, 32, 33). Animals were positioned supine in the EBCT gantry so that the heart was centered in the imaging field and fixed in the position for the subsequent studies. The field-of-view in the reconstructed tomographic images was 21 cm, pixel size of 0.58 mm, voxel size of 2.38 mm³, 7-mm slice thickness, acquisition time of 50 ms. Short axis images were obtained at four levels along the left ventricular (LV) axis (from apex to base), triggered at 80% of the RR interval.

Initially, a localization scan without any contrast agent was performed to determine the four LV levels. For the next scan, 4 ml of the low-osmolar, nonionic, radiopaque contrast agent (iopamidol, Isovue-370; Bracco Diagnostics, Princeton, NJ) was injected over 2 s selectively into the LAD catheter to highlight the LAD perfusion territory (Fig. 1, left), which then served as the region of interest for the analysis of the four subsequent flow scans obtained during an intravenous bolus injection of 0.33 ml/kg of iopamidol.

The four consecutive flow scan sequences were performed with a 20-min recovery period in between scans to allow washout of the extravascular contrast agent (8, 16) as illustrated in Fig. 2. These included a baseline study (intracoronary infusion of normal saline at 1 ml/min) followed by scanning sequences after 5 min of intracoronary infusion of adenosine (50 μg·kg⁻¹·min⁻¹; Sigma, St. Louis, MO), adenosine plus one selected diameter and dose of polymer microspheres (Duke Scientific, Palo Alto, CA), and at recovery (intracoronary infusion of saline at 1 ml/min). To assess the permeability response to varying magnitude of microembolization, we used microspheres of calibrated sizes and at one of three different doses (see Table 1) as previously shown (22, 27). The doses of microspheres were one-eighth, one-fourth, or one-half of the acutely
lethal dose for the selected microsphere diameter (26). Additionally, in 10 randomly chosen animals (1 animal for each size and dose of microspheres + 1 control), the EBCT cine mode was used, as described previously (31) (17 scans/series throughout several cardiac cycles), before and 20 min after embolization, to assess the diastolic thickness of the anterior wall and the total volume of the LAD perfusion territory as an index of myocardial edema following the coronary microembolization (1, 14, 28, 36). To distinguish the endocardial border from the contrast-filled LV cavity, the scans were obtained during continuous infusion of iopamidol. This contrast agent has a molecular weight of 777.09 kDa, the solute has an iodine concentration of 370 mg/ml, osmolality of 780 osmol/kg, viscosity of 9.1 mPa/s, and pH of 6.5 to 7.5. The endocardial and epicardial borders were then manually traced at end diastole, and LV muscle mass was calculated as the product of myocardial muscle area, myocardial specific density (1.05 g/ml), and slice thickness.

To ensure that the measurements of the wall thickness were performed in the same location within the myocardium before and after embolization, markers such as the diagonal branches of the LAD were used as fiducial markers as described previously (22, 23). Hemodynamic parameters, such as heart rate and arterial blood pressure, ECG, and body temperature, were continuously monitored. Continuous variables are presented as mean ± SD, unless indicated otherwise. A two-factor ANOVA with replication was applied for differences within the group at different scan conditions, and, if significant F values were obtained, Tukey honestly significant difference test was used for the post hoc analysis to identify both within-group and between-group differences. To express the relationship between the nonperfused myocardial volume and the total surface area of nonperfused myocardium (independent factors) and the increase in microvascular permeability (dependent factor), the Pearson correlation coefficients were calculated, and the linear regression analysis was used. P < 0.05 was considered significant.

RESULTS

In 30 animals (3 animals per each size and dose of microspheres + 3 control animals) the EBCT and micro-CT studies could be performed successfully. Four animals were lost due to refractory ventricular fibrillation after the microspheres injection.

Hemodynamic parameters. Hemodynamic parameters at baseline and after embolization with the different sizes and doses of microspheres are presented in Table 1. Heart rate increased in all animals significantly after embolization with microspheres, regardless of the size or dose (P < 0.01 vs. baseline) but remained unaltered in the control group. Mean aortic blood pressure only changed significantly in animals embolized with microspheres (µm/sph) of 100-µm diameter at the one-quarter and one-half fatal doses (see Table 1).

<table>
<thead>
<tr>
<th>Size and No. of µmph</th>
<th>Heart Rate, beats/min</th>
<th>Mean Arterial Blood Pressure, mm/Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Post-ME</td>
<td></td>
</tr>
<tr>
<td>10 µm, 1.25 × 10⁶</td>
<td>82 ± 5</td>
<td>91 ± 5*</td>
</tr>
<tr>
<td>10 µm, 2.5 × 10⁶</td>
<td>85 ± 18</td>
<td>100 ± 13*</td>
</tr>
<tr>
<td>10 µm, 5 × 10⁶</td>
<td>74 ± 17</td>
<td>85 ± 17*</td>
</tr>
<tr>
<td>30 µm, 3.75 × 10⁶</td>
<td>81 ± 12</td>
<td>95 ± 16*</td>
</tr>
<tr>
<td>30 µm, 7.5 × 10⁶</td>
<td>82 ± 7</td>
<td>95 ± 6*</td>
</tr>
<tr>
<td>30 µm, 1.5 × 10⁶</td>
<td>88 ± 16</td>
<td>109 ± 23*</td>
</tr>
<tr>
<td>100 µm, 1.25 × 10³</td>
<td>82 ± 15</td>
<td>99 ± 18*</td>
</tr>
<tr>
<td>100 µm, 2.5 × 10³</td>
<td>73 ± 14</td>
<td>90 ± 15*</td>
</tr>
<tr>
<td>100 µm, 5 × 10³</td>
<td>78 ± 9</td>
<td>101 ± 9*</td>
</tr>
<tr>
<td>Control, no µmph</td>
<td>93 ± 7</td>
<td>97 ± 6*</td>
</tr>
</tbody>
</table>

Data are presented as means ± 1 SD. Post-ME, after microembolization; µmph, microspheres. *P < 0.05 vs. baseline.
Table 2. Intramyocardial blood volume (Bv; ml/g myocardium) and regional myocardial perfusion (F = flow, ml.g myocardium⁻¹.min⁻¹) in the porcine left anterior descending coronary artery (LAD) perfusion territory at different scan conditions

<table>
<thead>
<tr>
<th>Diameter, No. of μm sph</th>
<th>Parameter</th>
<th>BL</th>
<th>IC AD</th>
<th>IC AD + μm sph</th>
<th>20 ± Post-ME</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 μm, 1.25 × 10⁶</td>
<td>F</td>
<td>0.97 ± 0.29</td>
<td>2.28 ± 0.40*</td>
<td>2.11 ± 0.37</td>
<td>1.11 ± 0.26*</td>
</tr>
<tr>
<td></td>
<td>Bv</td>
<td>0.11 ± 0.02</td>
<td>0.25 ± 0.05*</td>
<td>0.22 ± 0.03</td>
<td>0.13 ± 0.02†</td>
</tr>
<tr>
<td>10 μm, 2.5 × 10⁶</td>
<td>F</td>
<td>1.02 ± 0.24</td>
<td>2.09 ± 0.45*</td>
<td>1.66 ± 0.42*</td>
<td>1.13 ± 0.36*</td>
</tr>
<tr>
<td></td>
<td>Bv</td>
<td>0.12 ± 0.03</td>
<td>0.23 ± 0.04*</td>
<td>0.20 ± 0.04*</td>
<td>0.12 ± 0.03*</td>
</tr>
<tr>
<td>10 μm, 5 × 10⁶</td>
<td>F</td>
<td>0.95 ± 0.28</td>
<td>2.17 ± 0.45*</td>
<td>1.40 ± 0.26*</td>
<td>1.10 ± 0.38*</td>
</tr>
<tr>
<td></td>
<td>Bv</td>
<td>0.12 ± 0.03</td>
<td>0.24 ± 0.04*</td>
<td>0.15 ± 0.03*</td>
<td>0.12 ± 0.02*</td>
</tr>
<tr>
<td>30 μm, 3.75 × 10⁴</td>
<td>F</td>
<td>1.00 ± 0.27</td>
<td>2.33 ± 0.37*</td>
<td>1.62 ± 0.31*</td>
<td>1.12 ± 0.14*</td>
</tr>
<tr>
<td></td>
<td>Bv</td>
<td>0.12 ± 0.02</td>
<td>0.22 ± 0.02*</td>
<td>0.18 ± 0.03*</td>
<td>0.14 ± 0.02†</td>
</tr>
<tr>
<td>30 μm, 7.5 × 10⁴</td>
<td>F</td>
<td>0.95 ± 0.24</td>
<td>2.18 ± 0.39*</td>
<td>1.41 ± 0.49*</td>
<td>1.20 ± 0.29*</td>
</tr>
<tr>
<td></td>
<td>Bv</td>
<td>0.11 ± 0.02</td>
<td>0.23 ± 0.05*</td>
<td>0.16 ± 0.03*</td>
<td>0.13 ± 0.02†</td>
</tr>
<tr>
<td>30 μm, 1.5 × 10⁵</td>
<td>F</td>
<td>0.97 ± 0.25</td>
<td>2.11 ± 0.56*</td>
<td>1.32 ± 0.45*</td>
<td>1.13 ± 0.35*</td>
</tr>
<tr>
<td></td>
<td>Bv</td>
<td>0.11 ± 0.02</td>
<td>0.23 ± 0.05*</td>
<td>0.14 ± 0.03*</td>
<td>0.13 ± 0.03†</td>
</tr>
<tr>
<td>100 μm, 1.25 × 10³</td>
<td>F</td>
<td>1.90 ± 0.35</td>
<td>2.70 ± 0.41*</td>
<td>1.57 ± 0.56*</td>
<td>1.11 ± 0.22*</td>
</tr>
<tr>
<td></td>
<td>Bv</td>
<td>0.11 ± 0.03</td>
<td>0.23 ± 0.05*</td>
<td>0.17 ± 0.04*</td>
<td>0.13 ± 0.03†</td>
</tr>
<tr>
<td>100 μm, 2.5 × 10³</td>
<td>F</td>
<td>1.05 ± 0.31</td>
<td>2.38 ± 0.37*</td>
<td>1.34 ± 0.43*</td>
<td>1.12 ± 0.28*</td>
</tr>
<tr>
<td></td>
<td>Bv</td>
<td>0.13 ± 0.02</td>
<td>0.25 ± 0.06*</td>
<td>0.14 ± 0.05*</td>
<td>0.13 ± 0.03</td>
</tr>
<tr>
<td>100 μm, 5 × 10³</td>
<td>F</td>
<td>0.98 ± 0.30</td>
<td>2.24 ± 0.42*</td>
<td>1.03 ± 0.30*</td>
<td>0.06 ± 0.04*</td>
</tr>
<tr>
<td></td>
<td>Bv</td>
<td>0.12 ± 0.04</td>
<td>0.23 ± 0.04*</td>
<td>0.12 ± 0.04*</td>
<td>0.11 ± 0.03</td>
</tr>
<tr>
<td>Control, no μm sph</td>
<td>F</td>
<td>1.09 ± 0.23</td>
<td>2.22 ± 0.21*</td>
<td>2.10 ± 0.27</td>
<td>1.16 ± 0.26*</td>
</tr>
<tr>
<td></td>
<td>Bv</td>
<td>0.12 ± 0.02</td>
<td>0.22 ± 0.02*</td>
<td>0.22 ± 0.04</td>
<td>0.12 ± 0.05*</td>
</tr>
</tbody>
</table>

Values are presented as means ± 1 SD. BL, baseline; IC AD, intracoronary adenosine; μm sph, microspheres. *P < 0.05 vs. previous scan; †P < 0.05 for Post-ME vs. BL scan.

EBCT studies. Myocardial blood flow and blood volume at baseline and after coronary microembolization in relation to different sizes and doses of microspheres at different scan conditions are illustrated in Table 2. In all animals, flow and blood volume were comparable at baseline (P > 0.05) and increased significantly after intracoronary infusion of adenosine (P < 0.01). Embolization decreased blood flow and blood volume proportional to the sizes and dose of the injected microspheres (Table 2).

The index of permeability at baseline was similar among all animals (P > 0.05, Table 3). It remained unchanged during vasodilation with adenosine infusion but increased significantly (P < 0.01) after embolization in the LAD perfusion territory. In contrast to the LAD perfusion territory, permeability remained unchanged in the nonembolized LCX perfusion territory (P > 0.05). The highest increase in permeability in percentage compared with baseline value was observed after embolization with microspheres of 10-μm diameter, followed by 30 μm and 100 μm (Fig. 3), indicating an inverse relationship between the diameters of embolized vessels and the resulting increase in permeability.

Muscle volume of LAD perfusion territory and diastolic anterior wall thickness. Except for the control animal, the average volume of LAD perfusion territory, as an indicator of myocardial edema, increased significantly (P < 0.01) in all representative animals after embolization (Fig. 4A). Diastolic thickness of the anterior wall was 5.87 ± 0.19 mm and increased at 20 min after embolization to 6.56 ± 0.35 mm (P < 0.01), while the systolic thickness did not change (8.61 ± 0.30 mm vs. 8.55 ± 0.33 mm, P = 0.63). The increase in diastolic thickness of the anterior wall was highly correlated to...
the total surface area of the nonperfused myocardium (Fig. 4B, $r = 0.82$, $P < 0.01$).

**Micro-CT findings.** The volumes of nonperfused myocardial and the corresponding surface area of the embolization islands are presented in Fig. 5, A and B. The EBCT-derived increase in microvascular permeability for iopamidol following embolization was well correlated with the total surface area of the nonperfused myocardium ($r = 0.83$, $P < 0.01$, Fig. 5A) but showed weak correlation to the total nonperfused myocardial volume ($r = 0.43$, $P = 0.04$, Fig. 5B). By linear regression analysis, the microvascular permeability was related highly significant ($P < 0.001$) to the total surface area but not to the nonperfused myocardial volume ($P = 0.44$).
DISCUSSION

This study demonstrates that coronary microembolization with microspheres results in enhanced coronary endothelial vascular permeability in the embolized LAD perfusion territory. The lack of increase in permeability in the nonembolized LCX perfusion territory supports our first hypothesis that the increase in permeability is due to microembolization. Our second hypothesis, that the surface area of the interface between the nonperfused and perfused myocardium is the primary location of increased permeability, is supported by the high correlation between the increase of microvascular permeability and the total surface area of embolized, nonperfused myocardium (Fig. 5A). Similarly, the increase in diastolic wall thickness in vivo, and thereby the increase in volume of LAD perfusion territory, as an index of myocardial edema, is highly correlated to the total surface area of the embolized myocardial territories ex vivo (Fig. 4B).

In this study, we found that increased permeability is proportional to the total surface area of perfusion defects. For the same dose of different sizes of microspheres, the increase in permeability was more pronounced in animals embolized with smaller-sized microspheres (Fig. 3). One of the possible mechanisms may stem from the geometric relationship of the surface area-to-volume ratio of perfusion defects that decreases as N^{(-0.67)}, where N is the number of perfusion defects. However, this difference cannot solely be explained by the difference in the total surface area, since the increase in permeability exceeded by far the difference in the surface area. For instance, the surface area of nonperfused myocardium secondary to embolization by the highest dose of 10 μm microspheres was slightly higher than that caused by the 100 μm microspheres (Fig. 5A), but the increase in permeability was for the 10 μm microspheres twofold of that for the 100 μm. Addressing the pathophysiological mechanisms for the observed differences in permeability when blocking different-sized coronary microvessels is beyond the focus of this study; however, it is reasonable to assume that blocking of the 10-μm exchange vessels would affect more directly the physiology of exchange vessels, resulting in greater increase of permeability, whereas the blockage of the upstream 100-μm conduit vessels would result in larger individual nonperfused territories but would have less effect on permeability, since the downstream 10-μm vessels do not receive contrast to leak. Notably, the change of permeability in vivo, an important element of physiological coronary microvascular function, exhibited in this study an inverse relationship with the size of the embolized coronary arterioles. Our observation is consistent with a longitudinal gradient in metabolic, myogenic, and flow-induced responses to various physiological and pharmacological stimuli in coronary microcirculation as previously described by other investigators using an in vitro approach (19).

Increase of vascular permeability results in enhanced movements of fluids and solutes (39), as well as inflammatory mediators, from the intravascular into the interstitial and/or intracellular compartment, leading to change of cellular and extracellular osmolarity, disturbance of cell membrane conductivity, cell swelling, and interstitial edema (38), thereby compromising myocardial contractile function and potentially leading to lethal arrhythmias (12, 38). Inflammatory mediators such as TNF-α, free oxygen radicals, and interleukins have been shown to play a major role in contractile dysfunction in the microembolized myocardium following coronary microembolization (15, 17, 34), possibly indicating the role of inflammation and/or edema in its pathogenesis. Such mediators can likely more easily diffuse into the perfused myocardium from the interfacial region between perfused and nonperfused myocardium (i.e., proportional to the interface’s surface area) rather than from deep within the nonperfused myocardium, which would make the effect more proportional to the volume of nonperfused myocardium.

Increased permeability is a characteristic consequence of coronary endothelial dysfunction and is considered a major pathogenic mechanism in atherosclerosis (40). However, this important index of microvascular integrity is difficult to assess noninvasively and longitudinally in the beating heart. Our CT methodology enables sequential evaluation of regional myocardial microvascular permeability to X-ray contrast media. Using this method and a similar model of coronary microembolization, we have previously shown that microembolization resulted in a contiguous spectrum of perfusion defects that were related to the number of injected microspheres (22). We further demonstrated that the total surface area in a given volume of embolized myocardium was related to the total number of perfusion defects and to the consequent regional myocardial contractile dysfunction (23). Nevertheless, the relationship between the surface area of myocardial perfusion defects and the increase in microvascular permeability following experimental microembolization remained unknown.

Indeed, this study suggests that the previously reported microembolization-induced contractile dysfunction (23, 34) may be related, at least in part, to myocardial edema resulting from increased permeability, as demonstrated by increased diastolic wall thickness and increased volume of myocardium within the LAD perfusion territory (Fig. 4A). The increase in diastolic wall thickness and in the volume of the LAD perfusion territory following embolization cannot be attributed to the volume of the injected microspheres, since the total volume of spheres injected in each animal was negligible (i.e., <3 mm³) compared with the increase in tissue volume, which was ≥5 cm³ (Fig. 4A). Unlike myocardial infarction due to occlusion of an epicardial artery, where the chronic increase in LV muscle volume in the remote and infarct border region is mainly attributed to compensatory myocyte hypertrophy, an immediate and transient increase in diastolic wall thickness following embolization strongly suggests a consequence of myocardial edema, since an interval of minutes between the onset of embolization and the observed effect (increase in diastolic wall thickness) is too short for the process of myocellular hypertrophy. Furthermore, the close correlation between the increased diastolic wall thickness and the total surface area of the nonperfused regions (Fig. 4B) in this study supports our primary hypothesis of the perfusion/nonperfusion interface surface area as the primary location for increased permeability to fluid and solutes.

Study limitations. Although the porcine coronary artery and coronary physiology resembles that of humans, microembolization by biological particles, as it occurs in a clinical setting, might have different and/or additional consequences compared with experimental coronary microembolization by essentially inert microspheres. It is likely that the increase in microvascular permeability due to ischemia and inflammation induced
by biological particles would be more pronounced than to inert microspheres. Nonetheless, the current study underscores that the physical obstruction by inert microspheres also leads to increased vascular permeability. It is conceivable that some of the larger vessels in this study were occluded by aggregate of smaller-sized microspheres, and/or that contiguous perfusion territories were embolized by individual microspheres, thereby perturbing the accurate relationship between the diameter of the occluded vessel and the extent of vascular permeability. In addition, we studied relatively young pigs, and vascular permeability may be partly age dependent (5, 11). Nevertheless, this animal study strongly suggests that patchy occlusion of the coronary microvasculature results in enhanced extravasation of fluids and solutes.

**Conclusion.** Experimental coronary microembolization results in an increase of vascular permeability primarily by increasing the capillary extraction at the interface between perfused and the nonperfused territories for fluid and solutes, such as for the nonionic contrast agent iopamidol. The increase in vascular permeability is highly correlated to the total surface area of the nonperfused myocardium, indicating that the increase in permeability is mainly due to increased leakiness of the microvasculature at the surface area of the individual ischemic islands and normally perfused myocardium.

**Perspectives and Significance**

Increased microvascular permeability, a key characteristic feature of endothelial dysfunction and a precursor of atherosclerosis, might result from exposure to cardiovascular risk factors, preceding clinical signs or detectable vascular remodeling processes. This is the first study in animal model not only illustrating the extent and the time course of the permeability following coronary microembolization but also showing that its magnitude is in proportion to the surface area of the interface between the perfused and nonperfused myocardial territories.

Exploring the pathophysiological mechanisms and consequences of altered coronary microvascular permeability in the sequelae of coronary microembolization might extend our understanding of phenomena, such as the discrepant relation of nonperfused myocardial volume to a magnitude of decrease in LV performance (22, 23), transient regional myocardial dysfunction, its functional recovery, and perfusion-contraction mismatch. This, in turn, may contribute toward identifying new therapeutic targets in patients at risk for coronary microembolization.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**REFERENCES**

23. Malayar NM, Lerman LO, Goss M, Beighley PE, Ritman EL. Relation of nonperfused myocardial volume and surface area to left ventricular...