Preservation of endothelial cell structure and function by intracoronary perfluorochemical in a canine preparation of reperfusion

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ABSTRACT To determine the effect of intracoronary perfluorochemical on endothelial cell structure and function, 16 dogs were randomized to receive either low-dose (15 ml/kg) intracoronary perfluorochemical (Fluosol-DA) or saline after 90 min of proximal occlusion of the left anterior descending coronary artery (LAD). The animals underwent reperfusion for 60 min with the introduction of perfluorochemical or saline 5 to 10 min after the onset of reperfusion. Endothelium-dependent coronary vasodilatory reserve was determined in vivo both at baseline and 1 hr after reperfusion by infusion of acetylcholine and then serotonin into the distal LAD bed in 12 animals (six in each group). Both agonists significantly increased regional flow measured by $^{133}$Xe washout in the two groups before occlusion, but at 1 hr after reperfusion only animals given perfluorochemical demonstrated a significant increase in flow. Vasodilatory reserve was assessed in vitro with cumulative dose-response curves to acetylcholine on LAD rings proximal and distal to the snare in all animals. These studies demonstrated a significant reduction in endothelial cell-mediated relaxation of epicardial arterial segments in the ischemic segment of control but not treated animals. Light microscopy revealed the presence of neutrophils within vessels in the ischemic zones in control animals only. Electron microscopy showed capillary obstruction by endothelial cell protrusions and neutrophil and red cell plugging in control animals in the ischemic region but an intact endothelium and predominantly unobstructed capillaries in treated animals. These findings suggest that the structural and functional endothelial damage after reperfusion may be prevented by the administration of intracoronary perfluorochemical after the onset of reperfusion. 


EARLY CORONARY REPERFUSION reduces infarct size and improves ventricular function in man and animals. However, certain biochemical and anatomic changes occur with reperfusion that may result in the conversion of reversibly injured myocardial cells to irreversibly injured cells. The role of the endothelium is of particular interest in this phenomenon. Capillary damage has been suggested to be a major contributing factor to the development of microvascular damage associated with obstruction of capillaries by endothelial cell swelling and red cell and neutrophil plugs.

We have previously demonstrated that intracoronary administration of the artificial blood substance, perfluorochemical (Fluosol-DA 20%; Alpha Therapeutic Corp., Los Angeles), soon after reperfusion significantly reduces infarct size and improves regional ventricular function in both the short- and long-term canine preparation. However, the mechanisms by which this drug salvages myocardium have not been investigated. We postulated that because of its small particle size and low viscosity, perfluorochemical may penetrate into the ischemic microvascular bed after reperfusion and potentially preserve the endothelium. The aim of this study was therefore to assess the effect of intracoronary perfluorochemical on endothelial cell structure and function in a 90 min occlusion-reperfusion canine preparation. Endothelial cells are known to modulate reactivity of the coronary bed to various en-
dogogenous compounds by the release of “endothelial derived relaxation factor” (EDRF), and this regulatory mechanism can be used as a measure of the functional integrity of the endothelium. In this study, endothelial function in both the arteriolar and epicardial coronary arteries of the ischemic bed was estimated by studying vasodilatory reserve in vivo and in vitro in animals treated with perfluorochemical and in control animals. Functional differences were also correlated with ultrastructural changes.

Methods

Experimental protocol. Mongrel dogs of either sex weighing 20 to 25 kg were quarantined for 2 weeks to ensure that they were free of common canine diseases. On the day of the experiment, animals were randomized to one of two treatment groups and anesthetized with 30 mg/kg intravenous pentobarbital, intubated, and ventilated with a positive-pressure respirator to maintain an arterial pH of $7.4 \pm 0.05$. Anesthesia was maintained during the study with a combination of 5 mg morphine and 5 mg IV diazepam. Electrocardiographic leads I, aVF, and aVL were continuously monitored. A sternotomy was performed and the heart was exposed via pericardiotomy. Animals were given 1 mg/kg IV lidocaine. The left anterior descending coronary artery (LAD) was carefully dissected, and a snare (surgical monofilament) enclosed in a polyethylene sleeve tubing (PE 320) was placed after the first diagonal branch and secured to the epicardium with two sutures.

A small pediatric feeding tube (PE 100) was also placed in a diagonal vessel just distal to the snare and heparinized. A No. 7F sheath was inserted via a cutdown into the right femoral artery, into which a No. 7F pigtail catheter was introduced to monitor aortic pressure continuously and left ventricular end-diastolic pressure intermittently. A No. 7F Gensini catheter was placed under fluoroscopy through the right jugular vein into the great cardiac vein, and its position was confirmed by oxygen saturation and by a 3 ml injection of contrast material. The catheter was carefully secured to the skin, and its position verified intermittently fluoroscopically. The animal was allowed to stabilize for 45 min before the experimental protocol was begun.

Baseline heart rate, blood pressure, left ventricular end-diastolic pressure, and oxygen saturations across the LAD bed were recorded. Baseline myocardial blood flow in the LAD distribution was determined by measuring the washout of a $^{133}$Xe bolus injected into an arterial line in the diagonal artery. $^{133}$Xe washout was measured with a 1 x 2 inch sodium iodide crystal and a single-hole, straight-bore lead collimator. Vascular reactivity was measured by an increase in regional myocardial blood flow in response to the agonists acetylcholine and serotonin. Pilot studies were performed in four dogs to determine the optimal vasodilatory doses of these agents. Acetylcholine at infusion rates of 1 to 3 $\mu$g/min and serotonin at 10 to 20 $\mu$g/min were found to produce greatest dilatation, although the specific dose within this range varied from animal to animal. Therefore acetylcholine at rates of 1, 2, and 3 $\mu$g/min and serotonin at rates of 10, 15, and 20 $\mu$g/min were infused via the diagonal branch for 5 min with a Harvard constant-infusion pump. A 3 to 5 min interval was allowed between infusion of the two agonists. $^{133}$Xe washout measurements were repeated after each infusion, allowing the calculation of regional myocardial blood flow at each dose.

After baseline measurements, a prophylactic dose of lido-
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\[ Y = \frac{A - D}{1 + \left(\frac{X}{C}\right)^B} + D \]

where \( Y \) is the measured response, \( X \) is the arithmetic dose, \( A \) is the response at zero dose, \( B \) is a "slope factor" that measures the steepness of the curve, \( C \) is the \( E_{50} \), i.e., the dose producing a response midway between \( A \) and \( D \), and \( D \) is the response for "infinite dose." Since the variances over the range of doses used were not equal, the curves were fitted by a weighting coefficient, \( W_i \), which is inversely proportional to the predicted variance, \( \sigma_i^2 \), where:

\[ W_i = \frac{1}{\sigma_i^2} \]

where \( \sigma_i^2 = EY_i^2, Y_i \) is the response at dose, \( X_i \). The coefficients \( E \) and \( F \) were determined in a preliminary analysis of the data by fitting the measured variances to the corresponding responses. For the parameter estimates of the data grouped by location of the arterial segment, this was done on the data for that location only. With the segments compared to one another, the coefficients were computed for the entire data set.

The data for the artery segments were grouped by location and then fitted to the logistic dose-response equation to obtain the estimates of the fitted parameters (\( A, B, C, D \)) and their errors. The data for each segment location was then compared by a technique described by De Lean et al. In summary, the method permits the comparison of two or more dose-response curves with each other by permitting individual parameters of each of the fitted equations to be forced to be equal or held to a constant value. Goodness of fit is estimated with the "extra sum of the squares principle," using the residual variance as described by Draper and Smith. An \( F \) statistic was computed that measures the appropriateness of the constraints imposed.

Light and electron microscopy. One slice from the anterior wall of the left ventricle 2.5 to 3.5 cm below the site of the ligature of the LAD and one from the posterior wall of left ventricle were fixed in 10% buffered formalin. After paraffin embedding, sections were cut and stained with hematoxylin and eosin and examined under light microscopy for the presence of white cells within vessels and surrounding myocardium, in areas of ischemic (anterior) and nonischemic (posterior) zones. An average of 20 high-power fields (400 \( \times \) ) per slide were evaluated. The degree of neutrophil infiltration and extent of contraction band necrosis was assessed semiquantitatively according to the method of Romson et al. by a pathologist blinded to the treatment groups. A score of 4 + was assigned for the most dense infiltrate or amount of necrosis. Tissue samples were also taken for transmission electron microscopy from the ischemic and nonischemic areas, divided into endocardial and epicardial regions, and cut into 1 mm cubes fixed in 3% buffered glutaraldehyde for transmission electron microscopy. A total of 64 specimens were examined from eight (four perfluorochemical, four control) animals. Tissues were allowed to fix for 1 to 6 hr and then were transferred to 1% osmium tetroxide in 0.1M cacodylate buffer, dehydrated, and embedded in Epon. Semithin (0.5 to 1.0 \( \mu \)m) sections were cut, stained with toluidine blue, and examined by light microscopy. The artifact-free areas with the most capillaries were selected for ultrathin section cutting, stained with uranyl acetate lead citrate, and examined with a Zeiss 1091GF electron microscope.

Epicardial coronary artery segments from proximal and distal regions to the snare implantation were fixed in 3% buffered glutaraldehyde for examination by scanning electron microscopy. Tissue was dehydrated and critical-point dried with liquid carbon dioxide and visualized in a Philips 501B scanning electron microscope.

Statistics. Multiple groups were analyzed by two-way analysis of variance with BMDP software (BMDP2V, BMDP Software, Los Angeles) with a p value less than .05 required to reject the null hypothesis of equality. If a significant difference was found, pairwise comparisons were made by Duncan's multiple range test. To analyze the peak LAD flow in response to acetylcholine or serotonin, a paired Student t test and the Bonferroni correction was used with a p value less than .05 required to reject the null hypothesis of equality. All data in the text and figures are represented as mean \( \pm \) SEM.

Results

Twenty-four dogs were entered into the study. Four died of ventricular fibrillation during occlusion, and another four (two perfluorochemical, two control) were excluded because regional myocardial blood flow was not markedly diminished during occlusion (>33% of baseline flow). A total of 16 animals were included in the final analysis (eight perfluorochemical, eight control). In vivo data were available in 12 dogs (six in each group) and in vitro data were available in all animals.

Laboratory and hemodynamic variables (figure 1, A). No significant differences were observed in heart rate, systolic and diastolic blood pressure, mean arterial pressure, left ventricular end-diastolic pressure, or rate pressure product between the two groups throughout the study protocol. There were also no hemodynamic changes associated with intracoronary infusion of acetylcholine and serotonin into the distal LAD. Arterial \( P_O_2 \) at 1 hr after reperfusion was comparable in the perfluorochemical and control animals.

Regional myocardial blood flow (figures 1, B, and 2). No differences were noted between the two groups in regional myocardial blood flow, myocardial oxygen consumption, and coronary vascular resistance during the experimental protocol. Regional blood flow and myocardial oxygen consumption immediately after reperfusion in the perfluorochemical-treated animals had returned to values similar to baseline. However, in the control group, these variables remained significantly reduced compared with preocclusion values. By 1 hr after reperfusion, both perfluorochemical and control animals demonstrated a reduction of approximately 50% in regional blood flow and myocardial oxygen consumption compared with baseline. Coronary vascular resistance was not significantly increased from baseline in the treated group immediately and 1 hr after reperfusion. In contrast, the resistance remained slightly but significantly greater than baseline at these time points in the control group.

Vasodilatory reserve in vivo (figure 3). Before occlu-
FIGURE 1. Hemodynamic changes during experimental protocol. Measurements were obtained at baseline, 1 hr into occlusion (OCCl), 30 to 40 min after reperfusion (REPER), and 1 hr after reperfusion. A, No significant changes were noted in heart rate (HR) or rate pressure product (RPP). Left ventricular end-diastolic pressure (LVEDP) was significantly increased at reperfusion in both control and perfluorochemical-treated animals. B, Myocardial oxygen consumption (MVO2) and coronary vascular resistance (CVR). Note that CVR was not significantly different from baseline 30 to 40 min and at 1 hr after reperfusion in the perfluorochemical-treated group.

FIGURE 2. LAD flow measured by 133Xe washout in treated and control animals. After reperfusion, control animals demonstrated a significant decrease in regional flow compared with baseline, whereas in the perfluorochemical group no difference was noted. However, at 1 hr after reperfusion both groups had a significant reduction compared with baseline.

FIGURE 3. Regional myocardial blood flow responses in the LAD with agonists acetylcholine (ACH) and serotonin (SER). Before occlusion, a significant increase in flow occurred with each agonist in both perfluorochemical and control groups. However, 1 hr after reperfusion, only perfluorochemical-treated animals had a significant increase from baseline flow.
FIGURE 4. A. Comparative arterial vascular responses to acetylcholine in animals treated with intra coronary perfluorochemical and control. Note loss of relaxation response of control animal in ischemic (distal to snare) artery, whereas the vessel in the animal treated with perfluorochemical relaxes as well as the proximal (nonischemic) vessel. B and C. Curves fitted to experimental data for indicated segments and concentrations of acetylcholine, demonstrating a significant (p < .05) decrease in the ED₅₀ and slope factor in the distal control segment (ischemic vessel).

Light and electron microscopy (figures 5 to 8). Coronary arterial segments and myocardial biopsy samples in four randomly selected cases from the perfluorochemical group and four from saline control group were examined by light and electron microscopy. Light microscopy revealed marked differences in neutrophil accumulation within the ischemic myocardium between the two groups. Control animals demonstrated 2+ to 3+ neutrophils predominantly within capillary lumina and occasionally within adjacent myocardium, whereas neutrophils were rarely present (0 to 1+) in perfluorochemical-treated animals (figure 5). Contraction band necrosis was also more prominent in control (3+ to 4+) than in perfluorochemical-treated animals (1+ to 2+).

Electron microscopy of the endocardial regions in both control and treated animals showed changes of reversible and irreversible ischemic injury. Irreversible changes included shrunken nuclei, disruption of sarcolemmal membranes, and mitochondrial changes of clearing of matrix, fragmentation of cristae, and the presence of amorphous matrix densities. These changes were more severe in control animals. Reversible ischemic injury was more prominent in perfluorochemical-treated animals and included mitochondrial swelling, the loss of normal dense mitochondrial granules, and incomplete clearing of the mitochondrial matrix with absence of amorphous and granular flocculent densities within the mitochondria.

The capillary lumina in two control dogs contained membrane-bound bodies and endothelial protrusions (figure 6). Red and white cell plugging of capillaries was present in most control animals (figure 7). Endothelial cell disruption with the loss of pinocytotic vesicles was seen in all control animals (figure 7). A to C) often associated with platelet plugging and fibrin deposition. Perfluorochemical treated animals showed...
mostly an intact, swollen endothelium with prominent endoplasmic pinocytotic vesicles and endothelial folds (figure 8, A to C) in both reversibly and irreversibly injured regions of the myocardium. Occasional capillary disruption was also noted. Capillaries from perfluorochemical-treated animals rarely showed membrane bound vesicles (figure 8, D), and no luminal plugging by endothelial protrusions, white or red cells, or platelets was noted. Contracted sarcomeres were more often seen in control than in perfluorochemical-

![Photomicrographs of ischemic myocardium showing neutrophils within capillaries (arrows) in a control animal in A and B. Note absence of neutrophils within capillary (C) in a dog treated with intracoronary perfluorochemical after 90 min of ischemia and 60 min of reperfusion. (Hematoxylin and eosin; original magnification ×600).](image1)

![Ischemic area from the epicardial region of a control animal showing a capillary cut longitudinally. Note almost total absence of pinocytotic vesicles (arrows) and filling of the capillary lumen by endothelial protrusions (arrowheads), some cut longitudinally, others transversely (Original magnification ×20,000.).](image2)
treated animals. The capillaries in the nonischemic myocardium of control and treated animals were intact with occasional endothelial folds, and the myocardium showed no changes of reversible or irreversible ischemia. Perfluorochemical particles were not seen within necrotic myocytes or within inflammatory cells 1 hr after reperfusion in this preparation. Scanning electron microscopy of the epicardial coronary arteries showed no marked differences between control and perfluorochemical-treated animals. The endothelium was unremarkable except for occasional platelets, fibrin, and white cell adherence. Occasional segments showed endothelial disruption, probably attributable to handling of the coronary segments by instruments.
FIGURE 8. A. Fluosol-DA–treated animal showing irreversibly damaged ischemic endocardial region. There is evidence of severe swelling and clearing of mitochondria with disruption of cristae (arrow) within myocytes. B. The endothelial cells show minimal changes of edema and prominent pinocytotic vesicles and the cytoplasmic membranes are intact. C and D, Fluosol-DA–treated animal showing an arteriole within region of ischemic reversibly damaged myocardium. The endothelial cell contains vacuoles (C, arrow) and occasional endothelial folds (C, arrowheads) and a membrane-bound structure (D, arrow) in an animal treated with Fluosol-DA. (Original magnifications: A × 6600; B × 17,400; C × 12,000; D × 4500.)

Discussion

The endothelium and reperfusion. Reperfusion has been referred to as a “double-edged sword” because, although it is known to reduce infarct size, it may result in the death of potentially salvageable myocardium.6 Although the pathophysiologic basis of myocyte death after reperfusion is not well understood, several mechanisms have been considered.6, 7, 20, 21 Histologic analysis has shown that reperfusion results in marked disruption of the microvasculature, including capillary obstruction both by endothelial cell swelling and protrusions and by neutrophil and red cell plugs.6, 7, 21 Capillary changes in the permanent occlusion preparation are different with free-floating, intraluminal membrane-bound bodies and only occasional swelling of the endothelium.8, 9 Swelling and breakdown of the microvasculature after reperfusion may result in a progressive reduction in perfusion to potentially salvageable myocytes. This concept is supported in a recent study demonstrating a continual decrease in blood flow to areas of ischemic tissue after the onset of reperfusion.22

Endothelial cells are known to regulate the reactivity of the coronary vasculature to various endogenous compounds by the release of EDRF.12–14 Mechanical disruption of the endothelium abolishes vasodilation in response to acetylcholine and serotonin in vivo and in vitro.12, 13, 23 It has recently been shown that hypoxic and anoxic endothelial cells release vasoconstricting agents that may further reduce the capacity of the microcirculatory bed.24 The inability of reversibly damaged endothelial cells to release relaxing factors
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such as EDRF and prostacyclin into a vasoconstricted bed may contribute to the progressive decline in blood flow that occurs after successful reperfusion.\textsuperscript{22}

**Present study.** We postulated that perfluorochemical, because of its small particle size, low viscosity, and antineutrophil actions, may preserve endothelial structure and function in the ischemic zone after reperfusion and that this preservation may be an important mechanism for the enhanced salvage of ischemic myocardium previously reported.\textsuperscript{10, 11} A 90 min occlusion period was chosen because Klener et al.\textsuperscript{7} have previously shown that microvascular damage resulting in underperfusion of ischemic tissue occurs between 40 and 90 min of temporary occlusion. Since endothelial cell damage may be mediated by neutrophils, we also assessed the ability of the perfluorochemical mixture to inhibit neutrophil accumulation in ischemic zones.\textsuperscript{25-27}

Electron microscopy revealed greater preservation of endothelial cell structure in the ischemic subendoocardium in animals given intracoronary perfluorochemical compared with control when examined 1 hr after reperfusion. The structural abnormalities of the endothelial cells in the microvasculature of control animals were identical to those reported by Klener et al.\textsuperscript{7} These endothelial abnormalities included large intraluminal cell protrusions, decreased pinocytotic vesicles, and cell membrane disruption in association with platelet, fibrin, red cell, and neutrophil plugging. In contrast, the cytoplasmic membranes of the endothelium in perfluorochemical-treated animals remained relatively intact, with only mild swelling and without evidence of luminal plugging by endothelial protrusions or blood elements.

Since the method utilized for assessing endothelium-dependent vasodilatory reserve in this study had not been previously reported, pilot studies were initially performed. Once the approximate doses of the agonists were known, each animal underwent careful dose ranging at baseline to determine the maximal vasodilatory response with each agonist. Vasodilatory reserve was then determined 1 hr after reperfusion with the dose of the agonists that gave the maximal response before occlusion. These results revealed relatively preserved endothelium-dependent relaxation in perfluorochemical-treated animals only, as measured by an intact vasodilatory reserve in regional myocardial blood flow to the agonists acetylcholine and serotonin. These findings, in association with the maintained structural integrity, support our hypothesis that damage to the microvasculature is an important mechanism in the progressive decline in blood flow that occurs after successful reperfusion.\textsuperscript{22}

Cumulative dose-response curves to acetylcholine demonstrated a significant reduction in endothelial cell-mediated relaxation of epicardial arterial segments in the ischemic region of control animals. In contrast, distal segments of perfluorochemical-treated animals relaxed as well as segments located above the occluding snare in both treated and untreated animals. However, scanning electron microscopy revealed no structural differences in the endothelium of these arterial segments. These findings suggest that metabolic and/or biochemical changes precede structural changes in ischemic epicardial vessels. This study supports the hypothesis that regional ischemia first results in functional and then structural changes in the endothelium of the microvasculature, since epicardial vessels would be expected to have greater collateral flow and may therefore be more resistant to the effects of occlusion than arterioles and capillaries.

**Mechanisms of endothelial damage at reperfusion.** It has been proposed that damage to endothelial cells at reperfusion is mediated by free radicals and/or neutrophil-endothelial interactions.\textsuperscript{25-29} Some oxygen free radicals are reactive metabolites that are toxic to cellular components.\textsuperscript{28, 29} An increase in the intracellular and/or interstitial concentration of free radicals is known to occur within seconds after reperfusion.\textsuperscript{30} Since the perfluorochemical mixture was administered approximately 5 to 10 min after the onset of reperfusion and since we have previously shown that the perfluorochemical emulsion does not scavenge the superoxide anion in a cell-free system, it would appear unlikely that endothelial preservation in this study was caused by a reduction in free radical-mediated damage.\textsuperscript{31}

Although a continuous physiologic interaction normally occurs between neutrophils and the endothelium, hypoxic endothelial injury has been shown to augment neutrophil adherence in vitro.\textsuperscript{25} It has recently been proposed that complement activation caused by membrane disruption may mediate this increased neutrophil adherence.\textsuperscript{32} Both neutropenia and antileukocyte agents have been shown to reduce infarct size in reperfusion preparations.\textsuperscript{19, 33} Neutrophils adherent to the vessel wall may release toxic products that damage endothelial integrity or alter their function. Lysozomal enzymes such as elastase have been shown to digest vascular basement membranes in vitro and in vivo.\textsuperscript{26, 27} In addition, reactive oxygen metabolites produced by the neutrophil may disrupt endothelial membranes.\textsuperscript{27} Neutrophil-derived oxidants have also been shown to inactivate antiproteases present in serum.\textsuperscript{34} Neutrophil degranulation and free radical release may therefore

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permit an unchecked activity of various proteolytic enzymes on the endothelial cell membranes.

Mechanisms of endothelial preservation by perflurochemical. This laboratory and others have previously demonstrated that the perflurochemical mixture reduces neutrophil chemotaxis, adherence, and superoxide production in vitro. In a previous study, we have also shown that intracoronary perflurochemical does not alter peripheral white cell count measured 3 hr after reperfusion. Light microscopy in this study revealed infrequent neutrophils both within capillaries and the interstitium in the ischemic zones of the treated group at 1 hr after reperfusion. In contrast, neutrophils were abundant in control animals. By interfering with neutrophil-endothelial interactions (adherence) and/or by inhibiting neutrophil chemotaxis, the perflourochemical emulsion may have prevented neutrophil-mediated injury.

Because of its small particle size (average 0.2 μm) and low viscosity, perflurochemicals may deliver oxygen to endothelial cells in areas of the microcirculation inaccessible to red cells. Rude et al. demonstrated that perflourochemicals increase oxygen delivery to the border zones in a canine preparation of permanent occlusion. Enhanced oxygen delivery may have been responsible for the preservation of endothelial cell function within the ischemic myocardium as determined in this study by a maintained vasodilatory reserve in treated animals. Such preserved endothelial cell functions may include the release of vasodilatory compounds (e.g., EDRF and prostacyclin) and compounds that inhibit platelet clumping (prostacyclin).

Implications. The pathogenesis of reperfusion injury is still under investigation. An understanding of the anatomic and metabolic events occurring at reperfusion would have important clinical applications as newer and more potent thrombolytic agents have increased our ability to achieve reperfusion in patients with evolving myocardial infarction. We have previously shown that the intracoronary administration of perflurochemical soon after reperfusion significantly reduces infarct size, and this study demonstrates that the perfluorochemical preserves endothelial cell structure and function. These findings suggest that endothelial dysfunction may contribute to the death of potentially salvageable myocardium after successful reperfusion.

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