Assessment of Risk Area During Coronary Occlusion and Infarct Size After Reperfusion With Myocardial Contrast Echocardiography Using Left and Right Atrial Injections of Contrast

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Background. Myocardial opacification during echocardiography has been demonstrated after left (LA) and right (RA) atrial injections of contrast, and microvascular damage with reduced blood flow and impaired flow reserve has been documented in necrotic myocardial tissue. Therefore, we hypothesized that because of its ability to depict capillary perfusion, myocardial contrast echocardiography (MCE) can be used to define risk area during coronary occlusion and infarct size after reperfusion with LA and RA injections of contrast in the presence of pharmacologically induced coronary hyperemia.

Methods and Results. Eighteen open-chest anesthetized dogs with 3 to 6 hours of left anterior descending artery occlusion and 15 minutes of reflow were studied in the presence of either dipyridamole (0.56 mg/kg over a period of 4 minutes) or dobutamine (15 μg·kg⁻¹·min⁻¹). Technetium autoradiography was performed for risk area assessment; infarct size was measured with triphenyl tetrazolium chloride; and in 11 dogs, myocardial blood flow was measured with radiolabeled microspheres.

A close linear relation was noted between the MCE defect size and autoradiographic risk area during coronary occlusion both during LA (y=0.95x−0.25, r=.97, P<.001) and RA (y=0.90x+0.98, r=.86, P<.001) injections of contrast. During reperfusion, the contrast defect size on MCE was always less transmural than during occlusion and correlated closely with infarct size during both LA (y=1.07x−2.37, r=.98, P<.001) and RA (y=1.02x−0.61, r=.95, P<.001) injections of contrast. In the 11 dogs in whom radiolabeled microsphere-derived blood flow was measured during reperfusion, an inverse relation was noted between infarct size and transmural blood flow (y=−1.12x+121, r=−.95, P=.001), implying that MCE defects after reperfusion indicate necrotic regions with reduced blood flow or impaired microvascular flow reserve. A close linear relation (y=0.79x−0.001, r=.98, P<.001) was also noted between endocardial/epicardial ratio of background-subtracted peak video intensity on MCE and endocardial/epicardial blood flow ratio in the eight dogs with infarction who underwent this measurement after reperfusion.

Conclusions. MCE performed with LA and RA injections of contrast in the presence of pharmacologically induced coronary hyperemia can be used to determine, in vivo, the risk area during coronary occlusion and infarct size after reperfusion. These results could have important implications in this era of myocardial reperfusion. (Circulation 1993;88:596-604)

Key Words • echocardiography • occlusion • reperfusion • infarcts

The timely assessment of the extent of jeopardized myocardium, the success or failure of thrombolysis, and the degree of microvascular damage is of major clinical importance in patients with acute myocardial infarction. In a patient with chest pain thought to be ischemic in origin, it would be useful to know immediately whether the coronary artery is occluded and the extent of the risk area, since this information may determine how aggressive the therapy should be. Furthermore, if reperfusion is attempted in a given patient, knowledge regarding the amount of myocardium that has been salvaged would be of major prognostic importance.

Failure to reperfuse may be the result of persistent occlusion of the infarct-related artery. Even when arterial blood supply is restored, perfusion to the microvasculature may remain significantly reduced because of impairments in the structural integrity of the microvasculature (the "no-reflow" or "low-reflow" phenomenon). Infarcted tissue is also characterized by sustained reductions in microvascular flow reserve during reperfusion. These zones of either reduced blood flow or impaired microvascular flow reserve are located...
exclusively in irreversibly injured myocardium\(^5,6\) and occur in proportion to the extent and severity of cellular necrosis.\(^5,7\)

Because reduced blood flow and impaired microvascular flow reserve are hallmarks of myocardial necrosis during reperfusion, we hypothesized that an intravascular tracer of blood flow can be used not only to define risk area during coronary occlusion but also to determine infarct size after reperfusion. We tested this hypothesis using myocardial contrast echocardiography (MCE), which uses air-filled microbubbles that have an intravascular rheology similar to that of red blood cells.\(^9,10\) Abnormalities in microvascular reserve were elicited by use of pharmacologically induced hyperemia with intravenous infusion of either dipyridamole or dobutamine. We have previously demonstrated that these agents also enhance the ability to produce myocardial opacification from right atrial (RA) injection of contrast.\(^11\)

Methods

Animal Preparation

A canine model of 3 to 6 hours of coronary occlusion followed by 15 minutes of reperfusion was used. The protocol conformed to guidelines for animal research use at the University of Virginia. One dog with left atrial (LA) injection of contrast alone, nine with RA injection alone, and eight with both RA and LA injection were studied. All LA injections resulted in myocardial opacification. Since myocardial opacification from RA injection is not always successful,\(^11\) only dogs with successful opacification from RA injection of contrast at baseline were subjected to the entire protocol. The 17 dogs subjected to RA injection of contrast received either an intravenous infusion of 15 \(\mu\)g \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\) of dobutamine (Eli Lilly Corp, Indianapolis, Ind) (n=11) or 0.56 mg/kg of dipyridamole (Dupont Medical Products, Wilmington, Del) administered over a period of 4 minutes (n=6). Of these, 6 dogs receiving dobutamine (56%) and 5 receiving dipyridamole (84%) had successful myocardial opacification at baseline; only data from these dogs are presented here. These success rates for myocardial opacification from RA injections of contrast with these two pharmacological agents at these doses are consistent with our previous observations.\(^11\)

The dogs were anesthetized with 30 mg/kg sodium pentobarbital (Abbott Laboratories, North Chicago, Ill), intubated, and ventilated with a respirator pump (model 607, Harvard Apparatus, Natick, Mass). Additional anesthesia was administered during the experiment as needed. A 7F catheter was placed in the right femoral artery for recording of arterial pressure and withdrawal of reference samples for radiolabeled microsphere analysis. This catheter was connected to a multichannel recorder (model 4568C, Hewlett Packard, Everett, Mass) via a fluid-filled transducer (model 1280C, Hewlett-Packard). Another 7F catheter was placed in the left femoral vein for intravenous administration of fluids and drugs as needed.

A left lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery was dissected free from the surrounding tissues, and a tie with a snare was placed loosely around it. A 7F catheter was placed in the LA for injection of microbubbles, \(^99\)mTc-sestamibi, and radiolabeled microspheres. The RA was also cannulated with a similar catheter in dogs receiving RA injection of microbubbles.

Myocardial Contrast Echocardiography

MCE was performed using a phased array system (RTS5000, General Electric Medical Systems, Milwaukee, Wis) with a 5-MHz transducer. Gain settings were optimized initially and held constant throughout the experiment, and a maximal dynamic range of 72 dB was used. A saline bath served as an acoustic interface between the heart and the transducer. Imaging was performed at the midpapillary muscle short-axis level, and the data were recorded on 1.25-cm VHS videotape with a high-fidelity video recorder (Panasonic model AG6200, Matsushita Electrical Co, Japan).

Sonicated albumin microbubbles, custom-designed to our specifications by Molecular Biosystems, Inc, San Diego, Calif, were used as the contrast agent. For LA injections, 4 mL of bubbles with a mean diameter of 4.3±0.3 \(\mu\)m and a concentration of 0.5 billion/mL was used, whereas for RA injections, 10 mL of bubbles with a mean diameter of 3.7 to 5.3 \(\mu\)m and a concentration of 2.7 to 5 billion/mL was used. These bubbles were hand-injected as a bolus as previously described.\(^11\)

MCE images were analyzed with an off-line computer (Mipron, Kontron Electronics, Germany) as previously described\(^11,12\) and were transferred from videotape to image memory of the computer in a 244×244×8-bit format. Consecutive end-diastolic frames, encompassing the period from just before contrast injection until 8 to 10 seconds thereafter, were selected and aligned by use of computer cross-correlation techniques.\(^11,12\)

Because atrial injections of contrast result in relatively small changes in myocardial gray level, our approach to define perfusion defects was designed to highlight subtle gray-level changes.\(^11\) Two or three end-diastolic precontrast frames were averaged to improve the signal-to-noise ratio, and two or three contrast-enhanced end-diastolic frames were similarly averaged. The averaged precontrast frame was digitally subtracted from the averaged postcontrast frame. Each pixel in the digitally subtracted image manifesting an increase in video intensity was assigned a color, whereby gradations of red to orange, to yellow, to white represented increasing degrees of contrast enhancement. Pixels showing either no change or a decrease in gray level were not encoded with color, and the left ventricular cavity was masked out. During coronary occlusion, myocardial regions with absent color represented risk area, whereas during reperfusion, areas with relative color deficiency represented regions of reduced flow.

To determine the endocardial/epicardial video intensity ratios during reperfusion, regions of interest were placed over the endocardial and epicardial one third, respectively, of the occluded bed in the end-diastolic images.\(^13\) Video intensities within these regions were measured in the precontrast averaged images and subtracted from the postcontrast averaged images, and the ratios of these subtracted amplitudes from the endocardial and epicardial regions were calculated.\(^13\) The papillary muscles were not included in the endocardial regions of interest.
Technetium Autoradiography

Twenty millicuries of $^{99m}$Tc-sestamibi (Cardiolite, DuPont) were injected into the LA toward the end of the occlusion period to measure risk area. At the conclusion of the experiment, a short-axis slice corresponding to the plane of MCE imaging was cut from the excised heart as previously described. The slice was placed on double-emulsion x-ray film (X-Omatic AR, Eastman Kodak, Rochester, NY) that was exposed for 14 to 18 hours and developed with an automatic developer (model M35A, X-Omatic, Eastman Kodak). A back-illuminated image of the autoradiograph was captured into the off-line computer with a video camera with a resolution of 600 lines per field (66 series, Dage-MTI Corp, Michigan City, Ind.). The risk area, defined as the transmural defect on the autoradiograph, was planimetrized and expressed as a percentage of the myocardium in the short-axis slice.

Determinant of Infarct Size

The heart slice was immersed in a solution of 1.3% 2,3,5-triphenyl tetrazolium chloride (TTC) and 0.2 mol/L Sorenson’s buffer (KH2PO4 and K2HPO4 in distilled water, pH 7.4) at 37°C for 20 minutes and then fixed in 10% formalin. With this technique, noninfarcted areas stain brick red, and necrosed areas remain unstained. An image of the TTC-stained slice was captured into the off-line computer with the video camera, and the infarct, measured by planimetry of the nonstained area, was expressed as a percentage of the short-axis slice. The papillary muscles were not included in the estimation of infarct size.

Myocardial Blood Flow Measurement

Approximately 2x10⁴ 11-µm microspheres (Dupont Medical Products) suspended in 4 mL of 0.9% saline solution/0.01% Tween 80 were injected into the LA at each stage. Reference samples were withdrawn from the femoral artery over a period of 90 seconds using a constant-rate withdrawal pump (model 944, Harvard Apparatus). The short-axis slice of the left ventricle corresponding to the MCE image was cut into 16 wedge-shaped pieces after autoradiography and TTC staining, and each piece was divided into endocardial, midwall, and epicardial portions. The papillary muscles were not included in the endocardial portions. The tissue samples and the arterial reference samples were counted in a well counter with a multichannel analyzer (model 5986, AutoGamma Scintillation Counter, Packard Corp, Downer’s Grove, Ill). Corrections for activity spilling from one window to the next were made by use of a custom-designed computer program. Average transmural blood flows and endocardial/epicardial blood flow ratios within the occluded and nonoccluded beds were calculated by previously described methods.

Experimental Protocol

Baseline MCE was performed either 5 minutes after a 4-minute intravenous infusion of 0.56 mg/kg of dipyridamole or during an infusion of 15 µg·kg⁻¹·min⁻¹ of dobutamine. The proximal or mid portion of the left anterior descending artery was occluded for 3 to 6 hours to cause infarctions of various sizes. After occlusion, 100 mg of lidocaine hydrochloride (Abbott Laboratories) was given as an intravenous bolus, followed by a 2-mg/min infusion of the drug for the remainder of the experiment. Toward the end of the occlusion period, $^{99m}$Tc was injected into the LA, followed by MCE in the presence of either dipyridamole or dobutamine. The left anterior descending artery occlusion was then released, and after 15 minutes of reflow, radiolabeled microspheres were injected into the LA and MCE was performed in the presence of either dipyridamole or dobutamine. The dog was then killed by pentobarbital overdose, the heart was excised, and the slice corresponding to the image on MCE was processed to determine risk area by autoradiography, infarct size by TTC staining, and radiolabeled microsphere-derived myocardial blood flow.

Statistical Analysis

Data were expressed as mean±SD or as proportions. Comparisons between MCE and other measurements were made by linear regression analysis. Statistical significance was defined as P<.05 (two-sided).

Results

Left Atrial Injections

In one of the nine dogs receiving LA injection of contrast, data were not analyzed because of suboptimal quality of the images produced by entrapment of air between the saline bath and the anterior surface of the heart. Fig 1 illustrates an example of complete myocardial salvage after reperfusion in one of the remaining eight dogs. MCE during occlusion shows a 23% risk area, indicated by the anterior transmural relative color defect (panel A), which parallels the risk area on autoradiography (panel B). During reperfusion, contrast enhancement now occurs in this previously hypoperfused area (panel C), indicated by oranges and yellows. The TTC-stained slice shows no evidence of infarction (panel D). During these injections, although there is relative attenuation of the posterior segment of the heart caused by left ventricular cavity opacification, the borders of the defect can nonetheless be seen.

Fig 2 exemplifies a nontransmural infarction in another dog receiving LA injection of contrast. MCE and autoradiography concordantly show a transmural anterior defect (risk area) during left anterior descending artery occlusion (panels A and B, respectively). During reperfusion, the contrast defect persists, but it is no longer transmural (panel C). The subendocardial contrast defect corresponds to a nontransmural infarction indicated on the TTC-stained slice (panel D). Flow to the infarct zone during reperfusion was 64% of that to the nonoccluded bed in the presence of pharmacologically induced hyperemia, consistent with an impairment in microvascular flow reserve. The subendocardial character of the contrast defect parallels the reduced endocardial flow, which was only 21% of that to the epicardium in the presence of pharmacologically induced hyperemia.

Data for the eight dogs receiving LA contrast injection are summarized in Fig 3. Risk area varied from 15% to 43% of the myocardial short-axis slice. There was a close linear relation between MCE- and autoradiograph-derived measurements of risk area (panel A). After reperfusion, the contrast defects were less trans-
mural in extent, varying from 0% to 39% of the myocardial short-axis slice. Two dogs did not have detectable infarction. There was a close linear relation between MCE- and TTC-derived measurements of infarct size (panel B).

Right Atrial Injections

Fig 4 illustrates an example from one of the 11 dogs receiving RA injection of contrast in whom myocardial opacification was detected in all stages. After occlusion, there is homogeneous opacification of the left anterior descending arterial bed (panel A). The posterior half of the heart is attenuated because of the presence of contrast in the left ventricular cavity. MCE during reperfusion demonstrates a nearly transmural contrast defect (panel B), which parallels the infarct location and size on the TTC-stained specimen (panel C). Transmural flow to the infarct during reperfusion, in the presence of dipyridamole, was only 40% of the flow to the nonoccluded bed. In this example, therefore, less myocardial salvage is noted after reperfusion compared with the previous two examples with LA injection of contrast.

Results from the 11 dogs with successful myocardial opacification at all stages during RA injections of contrast are depicted in Fig 5. Risk area size ranged from 18% to 49%, and infarct size varied from 0% to 23% of the myocardial short-axis slice. There was a close linear relation between autoradiography and MCE-derived measurements of risk area (panel A). Similarly, the size of the residual contrast defect during reperfusion closely approximated TTC-determined infarct size (panel B). As in the dogs with LA injections, the size of the perfusion defect after reflow was always smaller than during coronary occlusion.

Myocardial Blood Flow

Radiolabeled microsphere-derived myocardial blood flow was measured in 11 dogs during reperfusion. There was a significant inverse relation between the size of the residual defect on MCE during reperfusion, expressed as percentage of the risk area, and blood flow to the risk area, expressed as percentage of flow to the normal bed (Fig 6, A). These results imply that contrast defects noted on MCE during reperfusion in the presence of pharmacologically induced hyperemia indicate regions with relatively reduced blood flow, impaired microvascular flow reserve, or both. When the ratios of background-subtracted peak video intensities from the endocardium and epicardium of the occluded bed during reperfusion were compared with the endocardial/epicardial blood flow ratios in the eight dogs with microsphere measurements who had TTC evi-
The ascending aorta, \( \text{Fig 2}. \) ours is the first study demonstrating that risk area can also be assessed by MCE using LA and RA injections of contrast.

The ability to assess risk area from RA injection of contrast has obvious clinical implications, since its detection confirms the presence of coronary occlusion and its size determines therapeutic options. For instance, one could aggressively attempt reperfusion if the risk area is large, whereas a small risk area may not require reperfusion, particularly if the hazards associated with therapy, such as bleeding complications, \(^{24-26}\) are high.

**Use of MCE for Determining Success of Reperfusion**

Kemper and colleagues\(^{23}\) were the first to demonstrate the ability of MCE to define infarct size after reperfusion. Although our results are similar to those of these authors, our study differs from theirs in four major respects. First, we measured infarct size after 15 minutes rather than 4 to 5 hours of reperfusion. In the clinical setting, confirmation of the success of reperfusion may be more relevant immediately after it is attempted rather than several hours later. Second, we injected contrast into the LA and RA rather than the aortic root. In patients with acute myocardial infarction, the assessment of risk area and success of reperfusion would be more useful from a peripheral venous rather than the ascending aorta.
than an aortic injection. The success of MCE from RA injection makes successful myocardial opacification from a peripheral venous injection more plausible. Third, we used small albumin microbubbles (mean diameter, <6 μm), which do not change coronary or systemic hemodynamics, rather than large bubbles (12 to 100 μm) produced by the reaction of hydrogen peroxide and blood, which cause significant hemodynamic derangements. Fourth, we used pharmacologically induced hyperemia to produce a relative contrast defect not only within regions that had low flow but also regions with reduced microvascular flow reserve and thus likely to be necrotic. We have since demonstrated that dipyridamole infusion after reperfusion unmasks reduced microvascular flow reserve in regions with myocardial necrosis and defines the area in which myocardial salvage is not likely. We have also demonstrated that pharmacologically induced hyperemia enhances the likelihood of achieving myocardial opacification from RA injections of contrast, since it allows more microbubbles to enter the myocardium and thus be detected by ultrasound.

In our study, as in the one reported by Kemper et al., reperfusion invariably either resulted in the disappearance of a defect or, if a defect persisted, it was no longer transmural. In the context of an acute ischemic syndrome, therefore, successful reperfusion can be inferred if a transmural MCE defect seen after an intervention is no longer present after the intervention. Our results, like those of Kemper and colleagues, however, pertain only to the single-vessel occlusion model in which the occlusion has been completely reversed. Whether similar perfusion patterns will be seen in the presence of multivessel disease or in the presence of a significant residual stenosis that persists after reflow needs to be investigated. Be that as it may, the demonstration by MCE of a change in the perfusion pattern after compared with before reperfusion may in itself provide clinically useful information.

Even if the infarct-related artery is known to be patent, determining the actual extent of reperfusion achieved is also important. In patients with acute myocardial infarction and an open infarct-related artery, for example, Ito et al. have shown, using intracoronary injections of contrast, that those with preserved perfusion by MCE have better recovery of regional left ventricular function than those with persistent defects. In conjunction with pharmacologically induced hyperemia, the extent of microvascular reperfusion in such patients may be even more important, since it would not only demonstrate regions with restored flow but potentially also regions that are not viable.

**Value of MCE in Determining Infarct Size After Reperfusion**

The abnormal behavior of the microcirculation within necrotic myocardium forms the basis for the use of MCE in the estimation of infarct size. White and colleagues reported that during reperfusion, blood flow greatly increases to regions with predominantly viable tissue, whereas flow is redistributed away from necrotic zones, and Cobb and coworkers found that after 2 hours of coronary occlusion followed by reperfusion, flow was significantly reduced in regions showing the greatest necrosis. Vanhaecke et al. reported severe and permanent reductions in basal reflow and microvascular flow reserve only in irreversibly damaged myocardium after reperfusion. Concurrent ultrastructural studies have demonstrated severe capillary damage, endothelial necrosis, and intraluminal debris with mechanical obstruction confined to necrotic myocardium. Our own studies support these observations.

Because sonicated albumin microbubbles track red blood cells within the microcirculation, contrast enhancement during reperfusion should occur only in areas in which intact microvasculature enables microbubbles to enter myocardial tissue. Areas with low or negligible basal flow during reflow, therefore, would appear as contrast defects. Furthermore, regions with adequate resting flow but impaired flow reserve would have less contrast enhancement during reperfusion relative to normal beds in the presence of pharmacologically induced hyperemia, thus appearing as relative perfusion defects. We noted an inverse linear relation between infarct size and myocardial blood flow after reperfusion and found that regions with necrosis had either no flow or relatively reduced flow compared with normal beds in the presence of pharmacologically induced hyperemia.
Role of MCE in Determining Endocardial/Epicardial Flow Ratio

In models of myocardial ischemia not associated with infarction, unlike others,33,34 we previously reported that MCE performed during intracoronary injection of microbubbles cannot be used to assess the endocardial/epicardial blood flow ratio.13 Unlike the situation in myocardial infarction, the microvasculature is patent during ischemia. Since findings on MCE relate to flow/volume relations rather than just flow alone, if reductions in endocardial flow are accompanied by concomitant reductions in the number of patent vessels,35 the flow/volume relation and, hence, the MCE parameters may remain unchanged. During ischemia, the number of patent vessels may decrease because of either lower distending pressure or higher myocardial pressure caused by ischemia.

In the present study, MCE was performed only in the presence of pharmacologically induced hyperemia, and the bubbles were injected into the LA or the RA. Since pharmacologically induced hyperemia increases blood flow by increasing intravascular volume,36 regions with greater intravascular blood volume during hyperemia had greater numbers of bubbles. Consequently, the good correlation between endocardial/epicardial peak video intensity ratio and endocardial/epicardial blood flow ratio probably occurred because of a higher intravascular blood volume (which translates into greater microvascular density) in the epicardial versus endocardial regions. The data were too “noisy” to generate time/intensity curves and examine myocardial transit rates of bubbles in the endocardium and epicardium as could be done with an intracoronary injection.13

Taken together, the results of this and our previous study13 indicate that although MCE is not capable of defining the transmural distribution of flow in ischemia alone, in conjunction with pharmacologically induced hyperemia, it is capable of defining this distribution when microvascular injury is seen in association with subendocardial infarction.

Limitations of the Study

Pharmacological maneuvers used to achieve myocardial opacification from RA injection were not always successful. As in our previous experience,11 myocardial opacification was most likely (approximately 85% of the time) in the presence of intravenous dipyridamole. Although found to be safe in patients with coronary artery disease,37-39 even within 1 to 4 days after myocardial infarction, dipyridamole has not yet been approved by the Food and Drug Administration for use in the early phase of acute myocardial infarction in humans.

We used short-axis views of the heart, precluding assessment of the posterior bed because of attenuation resulting from left ventricular cavity opacification. Future studies using other imaging planes should enable evaluation of regional perfusion of the posterior bed. Because of subtle changes in video intensity in the myocardium, particularly from RA injection of contrast, we used image processing techniques such as alignment,
digital subtraction, and color coding. Although we used a broad dynamic range (72 dB), we were limited by commercially available ultrasound technology. Linear ultrasound to video intensity signal conversion, digital data acquisition, and greater sensitivity would have resulted not only in higher-quality images but potentially also in a greater success rate of myocardial opacification after RA injection of contrast. These developments are currently under way and should soon become available.

Finally, the no-reflow phenomenon may be a dynamic process closely linked to the duration of reperfusion, and the present study was not designed to examine this issue. Preliminary data from our laboratory suggest that MCE can be used to assess in real time the temporal changes in the no-reflow phenomenon after reperfusion.

Clinical Implications
Our results indicate that MCE, in the presence of pharmacologically induced hyperemia, can demonstrate in vivo the risk area after coronary occlusion and infarct size after reperfusion with LA and RA injections of contrast. As such, MCE has the unique potential to demonstrate in vivo the success of reperfusion efforts during myocardial infarction and the extent of myocardial salvage after successful reperfusion in humans.

These findings could have important implications in this era of interventional therapy.

Until recently, transpulmonary opacification of the myocardium had been difficult to achieve. We have, however, demonstrated successful myocardial opacification from RA injections of highly concentrated bubbles approximately 85% of the time using intravenous dipidamol in dogs. Although technical problems such as image quality, signal-to-noise ratio, and attenuation-induced artifacts need to be overcome, the results of the present study set the stage for the use of MCE using intravenous contrast injections to determine the consequences of reperfusion therapy in humans.

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