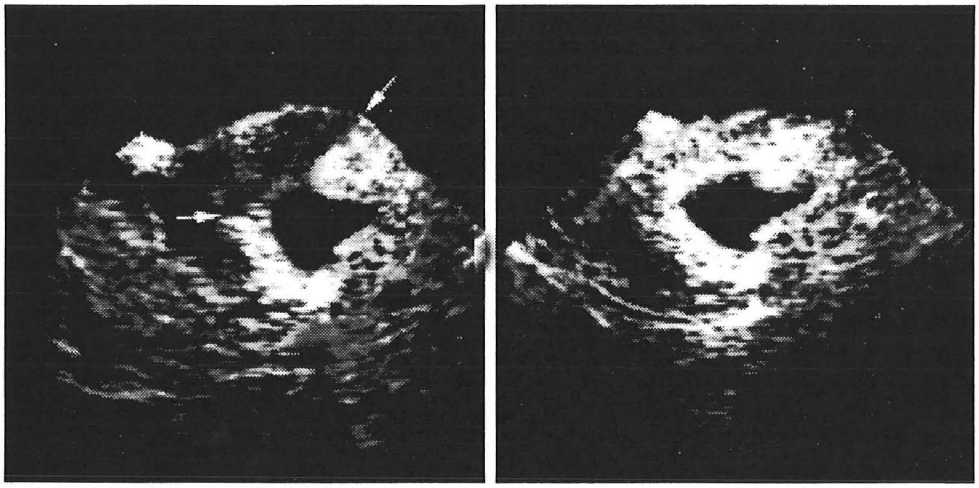
Assessment of Myocardial "Reperfusion" by Contrast Echocardiography

Paul A. Grayburn, MD



Coronary Artery Occluded
Perfusion Defect

Coronary Artery Open
Reperfusion

Internal Medicine Grand Rounds

University of Texas Southwestern Medical Center

August 28, 1997

Paul A. Grayburn, MD
Associate Professor of Medicine
Division of Cardiology

Research Interests:

- Prediction of outcome in congestive heart failure by echocardiography (BEST Trial Echocardiographic Substudy, NHLBI/VA Cooperative Studies, Co-Principal investigator with Dr. Eric Eichhorn)
- Development of fluorocarbon-based agents for myocardial contrast echocardiography (Principal investigator of several animal and human studies with funding from Sonus Pharmaceuticals, Molecular Biosystems, Inc, DuPont Merck Pharmaceuticals, Nycomed, Hewlett-Packard Medical Systems)
- Valvular heart disease (funding pending)
- Cardiovascular effects of cocaine in man (Co-investigator, NIDA grant 1 R01 DA10064-01, Dr. Ron Victor, Principal Investigator)
- Myocardial viability in patients with severely depressed LV function (Co-investigator, American Heart Association Texas Affiliate)

Case Presentation

KC is a 52 year old white man who presented to the Dallas VAMC with chest pain and 3-4 mm ST elevation in the anterior leads. His heart rate was 90, BP 100/64, RR 14, and he had normal JVP, bibasilar rales, an S4 gallop, no S3, no murmurs. He was treated with tPA approximately 6 hours after the onset of symptoms. Ninety minutes later, his chest pain had completely resolved but he continued to have 2-3 mm ST elevation anteriorly. He did not have any arrhythmias.

1) What is the likelihood of successful reperfusion in this patient?
   a) high
   b) low
   c) don't know
   d) don't care

2) Should the patient undergo coronary angiography to evaluate the efficacy of tPA and determine the need for salvage angioplasty?
   a) yes
   b) no
   c) don't know
   d) it depends on whether he has insurance or not

• • •

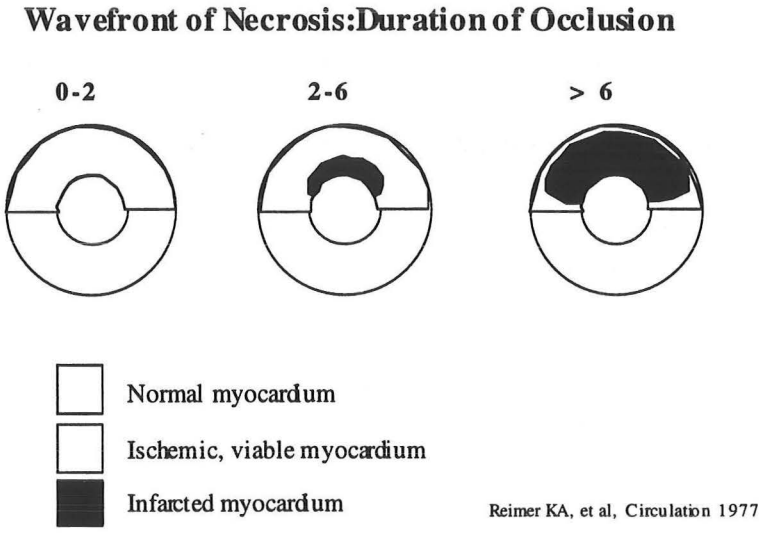
It is now well established that thrombolytic therapy for acute myocardial infarction (MI) improves patient survival and left ventricular function when given early after the onset of symptoms.[1,2] Primary angioplasty is an alternative to thrombolytic therapy that may be superior in high risk patients in institutions where it can be initiated promptly.[1-4] The two mechanisms by which early thrombolytic therapy or angioplasty exert their beneficial effects are:

1) opening the infarct-related artery (IRA), and
2) restoring tissue-level perfusion to the ischemic myocardium (reperfusion).

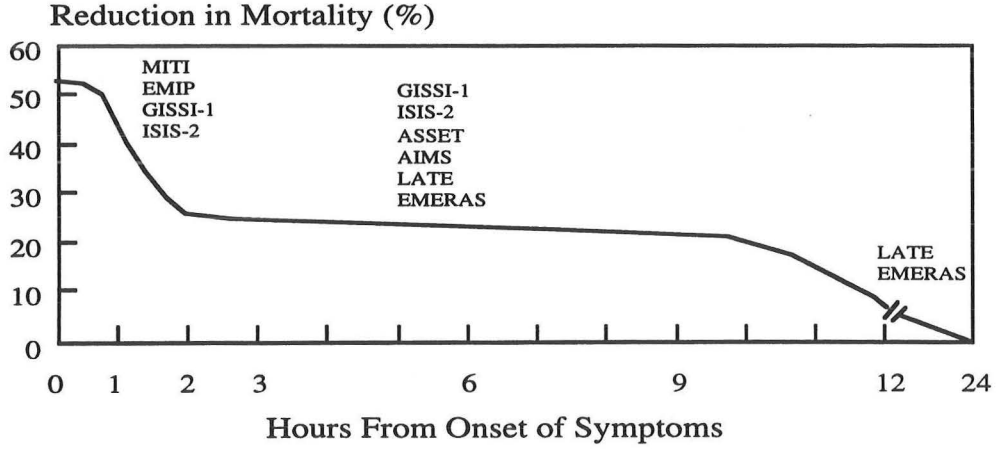
The term "reperfusion" is widely misused in the medical literature to refer to restoring patency to the IRA. Importantly, IRA patency and reperfusion are not equivalent and should not be used interchangably.[5] IRA patency is assessed by coronary angiography, the clinical reference standard for imaging large epicardial coronary arteries. However, the resolution of coronary angiography is not sufficient to image the coronary microcirculation where myocardial perfusion or reperfusion occurs. In this Grand Rounds, we will focus on the use of myocardial contrast echocardiography (MCE) to assess the status of the coronary microcirculation in patients with acute MI. MCE demonstrates that even though thrombolytic therapy and primary angioplasty often open the IRA, they do not always accomplish reperfusion. We will discuss the clinical implications of the disparity between IRA patency and reperfusion and the development of new intravenous contrast agents that can allow reperfusion to be assessed at the bedside by MCE.

Is it important to identify failed thrombolytic therapy?

One could argue that it is not important to identify failed thrombolytic therapy because the infarct-related artery (IRA) must be opened very early to restore perfusion to jeopardized myocardium. The classic study by Reimer and Jennings[6] showed that a wavefront of necrosis occurs as a function of the duration of occlusion. In figure 1, the LAD is occluded for a variable time period and then released. The extent of necrosis proceeds from subendocardium to subepicardium as a function of the duration of occlusion (wavefront of necrosis). No necrosis occurs for an occlusion lasting ≤ 20 min. For an occlusion ≥ 6 hours, transmural necrosis is extensive. Release of occlusion within 2 hours results in functional recovery of ischemic myocardium. Beyond 6 hours, there is little myocardium left to be salvaged. In humans, this time period may be longer due to the presence of collaterals, intermittent antegrade flow in the IRA, or ischemic preconditioning. Nevertheless, the thrombolytic trials provide compelling evidence that thrombolytic therapy must be administered very early for significant myocardial salvage to occur.



A consensus has now emerged that thrombolytic therapy is indicated in patients presenting within 12 hours of the onset of symptoms.[1,2] In fact, the greatest mortality benefit is seen in the first hour after onset of symptoms as shown in figure 2.[5] As can be seen, there is a 50% reduction in mortality with thrombolytic agents within the first hour. Between hours 2 - 10, the mortality reduction plateaus at around 25%. Beyond 12 hours, the survival benefit is minimal. Based on these data, one could hypothesize that by the time the patient presents to the Emergency Room, is evaluated, receives thrombolytics, and then undergoes an assessment of the success or failure of thrombolysis, it is too late to salvage a significant amount of myocardium.



On the other hand, a significant body of literature has emerged showing that a patent IRA late after acute MI is an independent predictor of a good prognosis. This "open artery hypothesis" states that IRA patency is beneficial to the patient independent of myocardial salvage secondary to early reperfusion.[7,8] One of the earliest studies to propose this hypothesis was a retrospective evaluation of 179 Parkland Hospital patients who had undergone coronary angiography late after MI and had single vessel disease of the IRA.[9] Over a followup period of nearly 4 years, none of 64 patients with a patent IRA died, whereas 21 of 115 (18%) patients with an occluded IRA died. Most of the deaths were sudden, presumably arrhythmic deaths.

Three large prospective studies have now demonstrated that the beneficial effects of an open IRA are independent of LV function.[10-12] White, et al[10] studied 312 consecutive patients with a first MI treated with thrombolytic therapy in New Zealand. Cardiac catheterization was performed at 28 ± 11 days and IRA patency established by the TIMI grading system and by an occlusion score that estimated the amount of myocardium supplied by the occluded IRA. The most important predictor of mortality on multivariate analysis was LV function. However, the IRA occlusion score provided prognostic information that was independent of LV function. Hohnloser, et al[11] studied 173 German patients with acute MI. Again, the best predictor of mortality was LV function but IRA patency exerted an independent progostic effect. Importantly, the best multivariate predictor of arrhythmia was IRA patency. Finally, the SAVE study evaluated the effect of captopril on survival in patients after acute MI who had a depressed ejection fraction (<40%). Of 946 patients in the SAVE study who underwent cardiac catheterization, IRA patency was an independent predictor of mortality by multivariate analysis ($p=0.039$).[12] Over a mean folloup period of 3.5 years, mortality was 12% in 784 patients with a patent IRA; 23% in 162 patients with an occluded IRA.

Although a patent IRA clearly is associated with a good prognosis after MI, it has not yet been proven that prognosis can be improved by mechanical restoration of antegrade flow in patients an occluded artery after MI. In a retrospective analysis of 200 survivors of acute MI with single vessel disease of the IRA,[13] there were 24 deaths (16%) in 148 patients treated medically compared to 1 death (2%) in 52 patients who underwent coronary revascularization for angina ($p=0.008$). Similar findings were present in 157 patients with multivessel disease;[14] mortality was 46% with medical treatment versus 18% with bypass surgery ($p=0.023$).

Should We Attempt to Open the IRA After Failed Thrombolytic Therapy?

There have been two prospective studies of rescue PTCA for patients with an occluded IRA after failed thrombolytic therapy (Table 1). The first of these was a small Canadian study of 28 patients randomized to rescue angioplasty or conservative management within 3 hours after failed thrombolysis.[15] Death occurred in 1/16 patients (6%) randomized to PTCA and 4/12 (33%) randomized to conservative therapy. The RESCUE trial was a larger trial of 151 patients with a first anterior wall MI who were randomized within 8 hours of failed thrombolysis.[16] The combined endpoint of death or severe CHF was significantly reduced in the PTCA group (6.4% versus 16.6%, $p=0.05$). Although these trials were not sufficiently powered to be conclusive, they suggest a survival benefit for this approach.

Table 1. Randomized studies of rescue angioplasty.

Study	n	timing	30 day mortality PTCA	30 day mortality no PTCA	p value
Belenkie[15]	28	3 hrs	1/16 (6%)	4/12 (33%)	NS
Ellis[16]	151	8 hrs	4/78 (5%)	7/73 (10%)	0.18

Despite the fact that a large, randomized clinical trial to test the open artery hypothesis has not yet been done,[7,8,17] it is now common clinical practice to attempt rescue PTCA for failed thrombolysis. One major difficulty with this strategy is that it requires accurate identification of patients in whom thrombolytic therapy has failed.

Clinical predictors of failed thrombolytic therapy

Unfortunately, clinical markers of successful thrombolysis, such as resolution of ST elevation, alleviation of chest pain, and the development of "reperfusion" arrhythmias, are not very helpful. Califf, et al[18] reported the ability of clinical markers to identify successful thrombolysis in the 386 patients enrolled in the TAMI trial. The customary endpoint of a patent IRA 90 minutes after thrombolytic therapy was used. The results are listed in Table 2. Complete resolution of ST elevation predicted a 96% likelihood of a patent IRA but this finding only occurred in 6% of patients. No single finding or combination of findings was able to adequately predict failure of thrombolytic therapy to open the IRA.

Table 2. Clinical predictors of IRA patency after thrombolytic therapy (TAMI Study).

Clinicalvariable	Percent of Patients	Percent with Patent IRA (95% CI)
ST Segment Elevation		
Unchanged	56	63 (56-70)
Improved	38	84 (76-90)
Resolved	6	96 (79-100)
Chest Pain		
Unchanged / Worsened	20	60 (48-71)
Improved	51	71 (64-78)
Resolved	29	84 (75-90)
Arrhythmia		
None	64	72 (65-78)
Ventricular Tachycardia	6	67 (45-84)
Idioventricular rhythm	7	75 (55-89)

Since clinical markers do not adequately identify the success of thrombolytic therapy, one could argue that all patients should undergo early catheterization post-MI to identify patients with a persistently occluded IRA who might benefit from PTCA. Several large randomized trials were performed to test this hypothesis and showed that routine catheterization and angioplasty early after thrombolytic therapy was not a useful strategy (Table 3).[19-23]

Table 3. Randomized Trials of Early Cath/ PTCA after Thrombolytic Therapy.

Trial	6 Week Mortality PTCA	6 Week Mortality Conservative	1 Year Mortality PTCA	1 Year Mortality Conservative
TIMI IIB[19,20]	5.2%	4.6%	6.9%	7.4%
SIAM[21]	8. 9%	6.0%	11.3%	9.0%
ESCG[22,23]	6.6%	2.7%	9.3%	5.4%
SWIFT[24]	3.3%	2.7%	5.8%	5.0%
TAMI 5[25]	5.6%	4.5%	8.4%	6.9%

Myocardial contrast echocardiography (MCE) is an emerging clinical tool that can accurately assess whether or not reperfusion has occurred post-MI. Figure 3 shows an MCE image from the patient presented earlier. Despite a patent IRA, a large apical perfusion defect is clearly seen on MCE. This brings up the obvious point that IRA patency does not equal reperfusion. This fact has now been demonstrated in several important studies which will be discussed. First, let us examine the reasons why IRA patency does not equate to reperfusion.

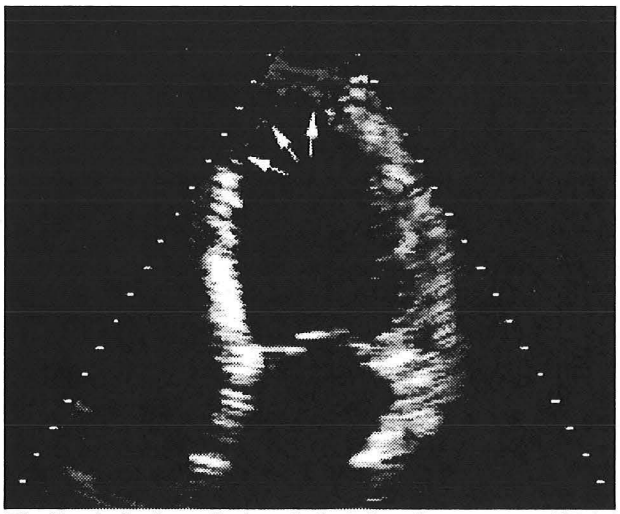


Fig 3. Apical perfusion defect despite a patent IRA with TIMI grade 3 flow.

Causes of Discrepancy Between Coronary Patency and Myocardial Perfusion

The No-Reflow Phenomenon. The classic example of a discrepancy between IRA patency and perfusion was first described in the dog model of acute myocardial ischemia by Kloner, et al.[26] In these studies, acute occlusion of the coronary artery was performed for 90 minutes followed by complete release of occlusion for 10 seconds to 20 minutes. Staining of the myocardium with thioflavin-S dye failed to show perfusion despite restoration of epicardial flow, a finding termed the no-reflow phenomenon. Histologically, the no-reflow phenomenon is characterized by severe capillary damage, myocyte necrosis, edema, plugging of the microvasculature with leukocytes, and evidence of oxygen-free radical damage (reperfusion injury).[26-29] The time course of the no-

reflow phenomenon varies from animal to animal and depends on the duration of occlusion, duration of restoration of post-ischemic epicardial flow, and the extent of collateral flow.

Collateral Flow. Another example of a discrepancy between IRA patency and myocardial perfusion is the presence of collaterals. In dogs, pre-existing epicardial collaterals ranging in size from 20 to 200 μm are capable of sustaining 5 to 10% of the resting myocardial perfusion after coronary occlusion.[30] Occasionally, capillary flow in dogs is sufficient to prevent wall motion abnormalities during coronary occlusion. In humans, capillaries tend to be smaller pre-capillary vessels more prominent in the subendocardium than subepicardium.[31] However, some patients are found to have occluded coronary arteries without wall motion abnormalities.[32] In such cases, well-developed epicardial collaterals are present, presumably from gradual, progressive stenosis of the coronary artery prior to occlusion.[30,31] The ability to promote collateral development by vascular growth factors, such as b-FGF or VEGF, has been a topic of much recent work.[33-35]

Myocardial Contrast Echocardiography: A Tool to Image the Coronary Microcirculation

Gramiak and Shah[36] first reported that indocyanine green injections produced a contrast effect on echocardiographic images. Since then, agitated saline has become widely used during echocardiography to assess right-to-left shunts.[37] MCE uses echogenic microbubbles that approximate the size of red blood cells and opacify the myocardium on two-dimensional echocardiography after intracoronary injection. The microbubbles are generally made in the catheterization laboratory by sonication of iodinated contrast material or alternatively, Albunex®, air-filled microspheres of 5% human albumin, can be used. Initial studies have documented the safety of MCE in humans.[38-40] Myocardial opacification by MCE occurs at flow rates down to about 15% of normal.[41-43] Thus, MCE is very sensitive in assessing myocardial perfusion. Unlike thallium-201 scintigraphy, MCE does not require active uptake by a functional cell membrane; it essentially provides an anatomic map of the myocardial microvasculature.

MCE in Acute MI: No Reflow Phenomenon. Several studies have examined the role of MCE in patients with acute MI. Ito, et al[44] showed that the no-reflow phenomenon, which has been well described in animal models of acute MI, also occurs in man. They studied 39 patients with acute anterior MI in whom the IRA was occluded angiographically and successfully reopened within 4 hours by either primary angioplasty (n=29) or intracoronary thrombolysis (n=10). MCE was performed during occlusion and after establishment of IRA patency. In 30 patients, myocardial reperfusion was evident by MCE after opening the IRA. However, in 9 patients (23%), the myocardial perfusion defect persisted despite achieving IRA patency (no-reflow phenomenon). In these 9 patients, LVEF measured 4 weeks later was worse than in the 30 patients with successful reflow (0.43±.09 vs 0.56±.13, $p<0.05$). This study was the first to demonstrate that the no-reflow phenomenon occurs in man. It also suggested that myocardial reperfusion is essential to recovery of LV function after early restoration of IRA patency.

MCE in Acute MI: Collaterals. Other studies have confirmed that myocardial perfusion by MCE predicts functional recovery after restoration of anterograde flow in patients with acute MI.[45-48] Sabia, et al[45] performed MCE during attempted PTCA of an occluded IRA in 43 patients. The time from onset of MI to PTCA ranged from 2 days to 5 weeks (mean 12 days). PTCA was successful in 32 patients, 23 of whom had good collateral perfusion by MCE, defined as ≥50% of the infarct bed perfused by injection into the noninfarct-related artery. One month after PTCA, wall motion score had improved in the 23 patients with good collateral perfusion but not in the 9 patients with poor collateral perfusion (Fig 4). Importantly, angiographic collaterals did not correlate with baseline wall motion or improve-ment in regional wall motion score index after PTCA. There was also a poor correlation between angiographic collaterals and collateral perfusion by MCE.

Ragosta, et al[46] studied 105 patients 1 to 4 weeks after acute MI. Following MCE, perfusion in each myocardial segment within the infarct zone was scored as 0- no perfusion, 0.5- patchy or subepicardial perfusion only, and 1- complete homogeneous perfusion). A contrast score index was derived by averaging the scores for the individual segments within the infarct zone. Of the 105 patients, the infarct-related artery was occluded in 57 and patent in 48. Revascularization was performed in 71 patients. By multivariate analysis, the single best predictor of wall motion score one month after MI was the contrast score index on MCE. Thus, perfusion was a better predictor of LV functional recovery than revascularization, baseline wall motion, infarct location, IRA patency, or any other clinical variable. Similar findings were reported by Camarano, et al[47] who found that perfusion within the infarct zone by MCE predicts subsequent recovery of LV function in patients who undergo late revascularization and by and Agati, et al[48] who found that perfusion of the infarct zone by MCE predicts late functional recovery in patients who do not undergo revascularization.

The above MCE studies confirm that in patients studied after acute MI, there is a discrepancy between IRA patency and perfusion. As in animal models, this discrepancy is caused by two major factors: 1) the no-reflow phenomenon, and 2) collaterals. Importantly, it should be understood that this is not an all-or-none phenomenon. In many cases, myocardium in the border zone of the infarct may be salvaged by opening the IRA with concomitant no-reflow and necrosis in the center of the infarction. All of the previous studies were performed using intracoronary injection of sonicated iodinated contrast or albumin-coated air microbubbles. This is not a feasible way to identify failed thrombo-lysis since it requires cardiac catheterization, a strategy that has been shown not to be useful in clinical trials.[19-25] Thus, new IV contrast agents capable of demonstrating myocardial perfusion are being developed.

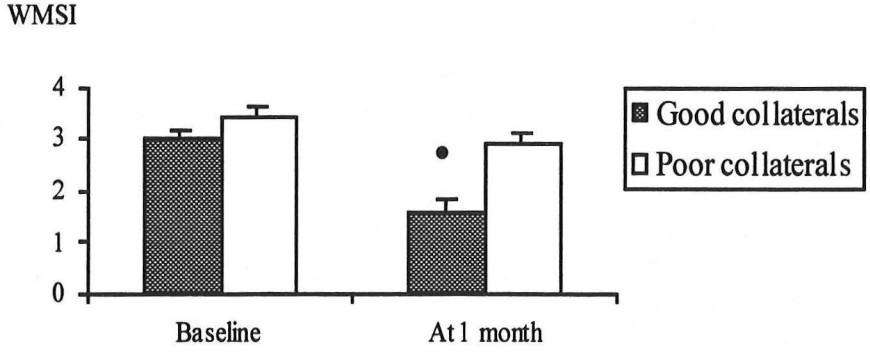


Fig 4. Change in wall motion score one month after PTCA in pts with collaterals by MCE

Novel Agents for Intravenous MCE

Echocardiographic signals are generated from differences in acoustic impedance such as occur between blood and soft tissue. Gas bubbles generate a strong ultrasound signal because of the marked difference in acoustic impedance between gas and blood. The intensity of the reflected ultrasound is proportional to the radius of the bubble to the sixth power.[49] Therefore, the larger the bubble, the greater the ultrasound signal. Conversely, the microbubbles should be smaller than red blood cells so that they do not occlude the microcirculation. When agitated saline is injected intravenously during echocardiography, the air microbubbles diffuse across the pulmonary alveolar capillary membrane such that air contrast is seen in the right-sided chambers but not the left-sided chambers. This phenomenon is widely used clinically to detect right-to-left shunts by echocardiography. In order for microbubbles to appear on the left side of the heart after intravenous injection, they must exhibit several characteristics:

1) low diffusivity across the pulmonary alveolar capillary membrane
2) low blood solubility
3) small enough microbubble size to cross the pulmonary microcirculation
4) biologically inert.

The first FDA-approved agent for left-sided contrast echocardiography was Albunex®, which is air-filled microbubbles of 5% human albumin.[50-52] This agent has not been successful at myocardial opacification, in part because it does not meet requirements 1 and 2 in the above list. In addition, Albunex® is prone to microbubble destruction by ultrasound.[53]

Saturated fluorocarbons meet all of the above characteristics and have become the mainstay of the new contrast agents being developed today. The following is a list of agents currently in clinical trials. FDA approval is expected within the year for at least two of these agents.

1. QW3600 (EchoGen®)- This agent is a 2% emulsion of dodecafluoropentane and has a boiling point of 29° C and therefore is a liquid at room temperature but a gas at body temperature. It has a mean microbubble diameter of 5-6 μm and a half-life in blood of up to 6 minutes. It is eliminated via expired air without metabolism.[54]
2. QW7437- Similar to EchoGen® but the particles are anionically charged to prevent microbubble adherence to the endothelium and to each other (bubble coalescence).[55]
3. FS069 (Optison®)- Similar to Albunex® except the albumin microbubbles contain perfluoropropane instead of air. Mean particle size is 3-4 μm. It has a very short half-life and is eliminated via expired air without metabolism.[56-58]
4. DMP115- Perfluoropropane microbubbles encapsulated in a lipid shell.[59]
5. Imagent®- Perfluorocarbon gas encapsulated in a polymer shell. It also contains a small amount of nitrogen and oxygen gas to prevent microbubble growth in the circulation as nitrogen and oxygen diffuse into the bubble.
6. BR-1- Sulfur hexafluoride gas encapsulated in a lipid shell
7. NC100100- Albumin-coated perfluorocarbon stabilized with sucrose.
8. Quantison®- Myocardial deposit agent yields persistent myocardial opacification after contrast clears from the LV cavity.

Use of Intravenous Perfluorocarbons to Assess Myocardial Perfusion

Initial animal studies. Grayburn et al[60] first demonstrated the ability of these agents to identify reperfusion and the no-reflow phenomenon after intravenous injection in the dog model of acute ischemia. A total of 15 dogs underwent occlusion of the left anterior coronary artery for 90 minutes, followed by release of the occlusion for 4 hours. Regional myocardial blood flow was assessed by radiolabeled microspheres. Echocardiography with intravenous 2% dodecafluoropentane emulsion was given at baseline, during occlusion, and after release of occlusion. After sacrifice, the heart was removed and sectioned using monastral blue dye to determine myocardial risk area and triphenyltetrazolium chloride (TTC) to identify infarct size. Some dogs demonstrated complete reperfusion of the risk area with little or no infarction (Fig 5). Others had substantial no-reflow phenomenon with nearly transmural infarction (Fig 6). Contrast echocardiography was able to accurately predict infarct size ($r=0.96$, $y=0.95x$ -1.2, SEE=9.7%). Other animal studies have confirmed the ability of various contrast agents to identify myocardial perfusion defects and reperfusion.[55-59]

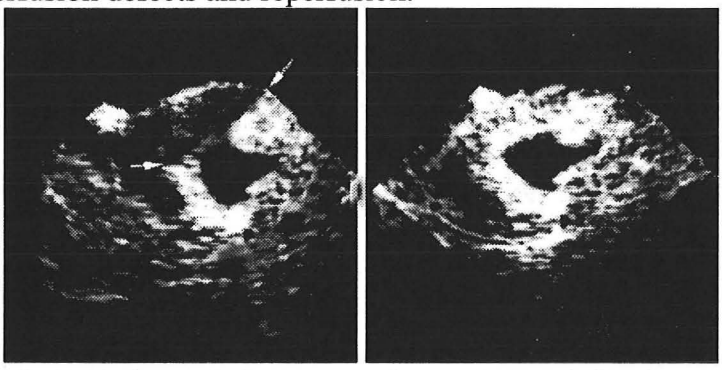


Fig 5. Left panel. Large anterior perfusion defect in a dog during LAD occlusion (arrows). Right panel. Reperfusion of anterior wall after release of 90 minute occlusion.

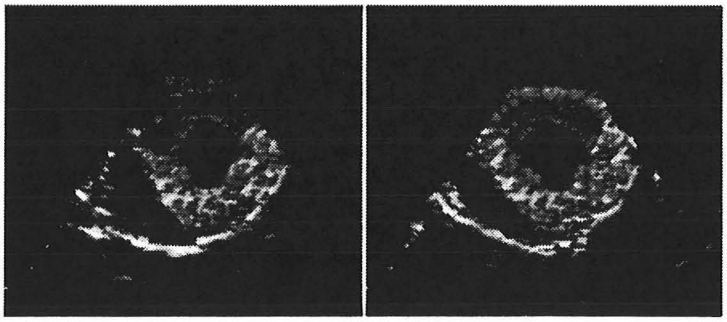


Fig 6. Left panel. Large anterior perfusion defect in a dog during the 90 minute LAD occlusion. Right panel. After release of occlusion, perfusion is still absent to most of the anterior wall (no-reflow phenomenon). A small rim of epicardium is perfused.

Developments in imaging technology. It has been difficult to reproduce the success of myocardial perfusion imaging with fluorocarbon-based agents in man during two-dimensional echocardiography. In a multicenter trial comparing EchoGen® to Albunex® in 254 patients, perfusion was evident in about 60% of patients with the former agent.[61] However, in most of these patients, perfusion was faint and difficult to see. One reason for this is the obvious difference in image quality between open-chest dogs and closed-chest humans. In addition, it has recently been shown that continuous bombardment of microbubbles with ultrasound tends to cause destruction of the microbubbles and subsequent image degradation. This has led to the development of intermittent ultrasound gated to the ECG.[62,63] Accordingly, end-diastolic or end-systolic imaging using one ultrasound pulse per cardiac cycle dramatically improves the ability to visualize myocardial perfusion in humans. This phenomenon appears to hold true for all current contrast agents.

Another development that has improved the ability to detect myocardial perfusion in man is second harmonic imaging.[64,65] When a sound wave reflects off of a bubble, it returns to the transducer at its transmitted frequency as well as at multiples of that frequency (harmonics). This harmonic response occurs to a much greater degree with microbubbles than with blood or tissue. Therefore, ultrasound transducers have been developed that transmit at a given frequency and receive at twice that frequency. For example, in our laboratory we are using a Hewlett-Packard instrument that transmits at 1.6MHz and receievs at 3.2MHz. This enhances the signals returning from the microbubbles relative to the tissue signals from the myocardium. By using a combination of intermittent imagingand second harmonics, myocardial perfusion in humans is now feasible.

Human studies of myocardial perfusion. Porter, et al[66] first validated myocardial perfusion by MCE in man by comparing it with SPECT thallium. MCE was performed with end-systolic harmonic imaging after administration of perfluorocarbon-exposed sonicated dextrose albumin in 25 patients. Rest and dipyridamole images were obtained and compared to dipyridamole SPECT thallium studies. The correlation between peak myocardial videointensity and regional thallium uptake was good (r=0.88).

Kaul, et al[67] studied 30 patients undergoing MCE and SPECT thallium imaging at rest and after dipyridamole. MCE was performed using end-systolic second harmonic imaging with FS069. MCE images were analyzed by digital subtraction of the post-contrast frames from a mask of 5 averaged pre-contrast frames. The background-subtracted images were then color-encoded to enhance the ability to visually identify perfusion defects. The concordance between SPECT thallium and MCE for assessment of myocardial perfusion is shown in table 4.

Table 4. Concordance between MCE and SPECT Thallium for Myocardial Perfusion.

Variable	Concordance	Kappa
Segmental perfusion score	92%	0.99
Segment normal, reversible, or fixed	90%	0.80
Vascular territories (LAD, Cx, RCA)	90%	0.77
CAD present or absent	86%	0.86

We are currently participating in a multicenter trial comparing intravenous MCE with 2% dodecafluoropentane emulsion (EchoGen®) to SPECT nuclear imaging in patients with a previous MI at least 30 days prior to enrollment. Fig 7 shows an example of an end-systolic image from the apical 4-chamber view showing a perfusion defect in the distal septum and apex in a patient with an old anterior MI. A perfusion defect in the same location was also present on a resting Tc-99 sestamibi SPECT image. The ability of MCE with intravenous fluorocarbon agents to identify perfusion defects in patients with an MI should enable the identification of patients in whom thrombolytic therapy has failed to achieve reperfusion. However, intravenous MCE will not allow us to determine whether the IRA is patent with no-reflow or occluded. On the other hand, resolution of a perfusion defect by MCE after thrombolytic therapy is likely to indicate that reperfusion has occurred as a result of IRA patency.

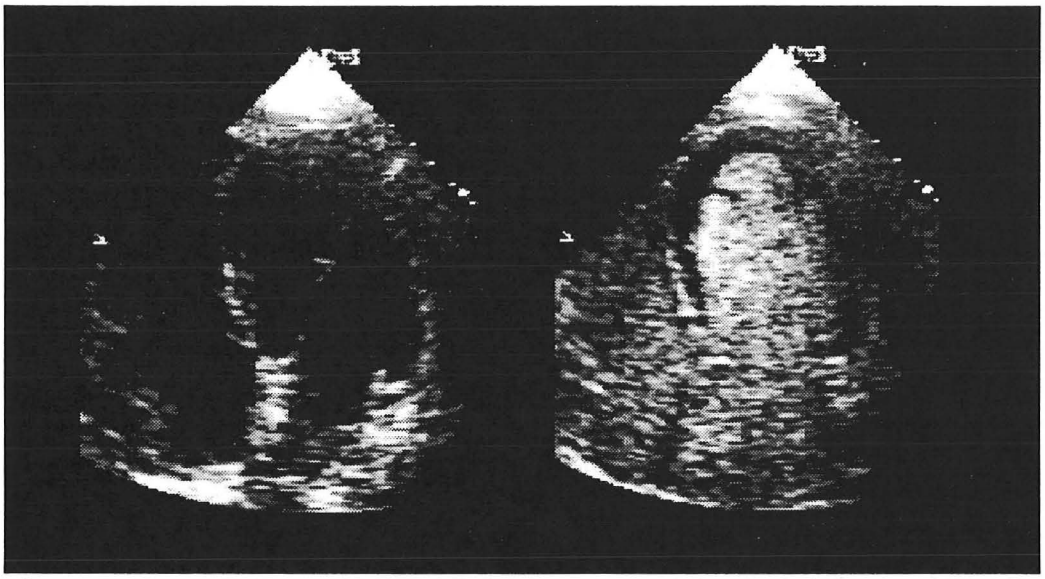


Fig. 7. Left panel. Second harmonic image prior to injection of contrast agent. Right panel. After contrast, a large perfusion defect is seen in the distal septum.

Future Directions

The ability of MCE to identify myocardial perfusion defects after acute MI offers the potential for bedside identification of patients in whom thrombolytic therapy has succeeded or failed. However, there are several unresolved issues that need to be addressed before this becomes routine practice. First, a large, randomized trial of the open artery hypothesis is needed. If it were to show that there is no benefit in opening the IRA after MI, the identification of failed thrombolysis might be irrelevant. Second, myocardial perfusion is a better predictor of left ventricular functional recovery than IRA patency. However, IRA patency has survival benefits that are independent of left ventricular function and may be related to reducing arrhythmogenic potential. It is not known whether such mortality benefit is independent of perfusion. Therefore, any trial of the open artery hypothesis should also attempt to answer the question of whether IRA patency or reperfusion is a better predictor of survival after acute MI.

The disparity between IRA patency and reperfusion indicates that current therapies to open an occluded IRA early after MI are not effective at preventing microvascular damage (no-reflow phenomenon).[5] Strategies to enhance the effectiveness of thrombolytic therapy with adjuvant drugs to enhance thrombus dissolution,[68-71] limit reperfusion injury,[72-74] promote angiogenesis,[75] etc may prove to be useful in increasing the number of patients who achieve true reperfusion after thrombolytic therapy for acute MI.

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