**Myocardial contrast echocardiography in acute myocardial infarction**

**Pathophysiological background and clinical applications**

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Myocardial contrast echocardiography is a technique used in experimental and clinical settings in order to visualize the pattern of intramyocardial perfusion. In the acute phase of myocardial infarction, regional absence of flow during myocardial contrast echocardiography delineates the area at risk of necrosis, while the definitive non-perfused area expresses infarct size. Reopening the infarct-related artery, which may be achieved spontaneously by thrombolysis or percutaneous transluminal coronary angioplasty, is not a reliable indicator of intramyocardial reperfusion. If myocardial ischaemia due to coronary occlusion has been sufficiently prolonged and severe, not only myocyte viability, but also microvascular integrity is lost. Myocardial contrast echocardiography, using intracoronary injection of sonicated contrast medium, gives information about microvascular integrity and the effective presence of intramyocardial reflow. Anatomical integrity of microvasculature does not necessarily imply preserved function, and thus the microvessel vasodilating reserve may also be impaired. Myocardial contrast echocardiography has the potential to assess alterations in microvascular function, showing, in the myocardial area with reduced coronary reserve, a relatively reduced increase in echocontrast signal intensity when an intravenous vasodilator agent is administered.

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**Introduction**

In acute myocardial infarction, the major determinant of functional damage is infarct size[1]. This, in turn, is determined by several factors: the extension of risk area (the myocardial area which will probably undergo necrosis)[2-3], the duration of anterograde blood flow abolition and the possible presence of concomitant situations (therapeutic and/or anatomical), such as successful early reperfusion of the infarct-related artery obtained by thrombolysis[4] or coronary angioplasty, or the presence of coronary collateral circulation[5,6], that can maintain a certain degree of myocardial viability within the risk area. Both early reperfusion and adequate collateral circulation favour blood flow supply to the myocardium during prolonged myocardial ischaemia, although through different vessels (infarct-related artery, another coronary artery), thus limiting the development of irreversible myocardial damage.

In the subacute phase of myocardial infarction, restoring blood flow through the infarct-related artery has been shown to be beneficial[7], and can even occur in patients in whom an infarct-related artery is reopened by percutaneous coronary angioplasty some weeks after myocardial infarction[8]. However, such functional recovery by angioplasty or coronary artery bypass grafting can be observed only in patients whose myocardial reperfusion is potentially adequate[8]; this potential recovery cannot be predicted by simple coronary angiography results, since the latter allows visualization of only large epicardial vessels and information on the condition of microvessels (and tissue perfusion) cannot be obtained unless digital technology and large computer applications are employed.

Recent studies have demonstrated that myocardial contrast echocardiography has an important role in this context since the contrast is a micro-vasculature tracer[8-13] it clearly delineates the risk area (as non-opacified myocardium) in the acute phase[14,15]. After
reperfusion, the extent of myocardium within the risk area in which the microvasculature has not been destroyed by prolonged ischaemia and which consequently may recover functionally if adequately reperfused (viable myocardium) can also be demonstrated.

Myocardial contrast echocardiography: technical background

Experimental studies have clearly demonstrated that the effectiveness of myocardial echocontrast depends on the presence of gas microbubbles inside the injected liquid.

Contrast echocardiography has been used not only to opacify cardiac chambers and to detect the presence of intracardiac shunts, but also to obtain information on myocardial perfusion by means of injection of contrast material into the coronary arteries. Since the contrast agents for myocardial perfusion remain intra-luminal and do not cross vessel walls, the vascular network acts as a scattering site.

The ideal requirements for an ultrasound contrast agent for myocardial perfusion may be summarized as follows: (1) it should have adequate echogenicity to change the contrast of the background with minimal doses; (2) it should provide low attenuation of the ultrasound beam; (3) it should be rapidly eliminated from the body; (4) it should be able to pass the pulmonary capillary bed; (5) it should be sufficiently stable to allow necessary measurements; (6) it should be easy to prepare and be reproducible; (7) it should be non-toxic; (8) it should have no effect on either coronary arteries or left ventricular function.

The agents which have been proposed so far have, to a greater or lesser extent, some limitations, due to the absence of one or more of the above requirements. The agent most commonly used in clinical studies is sonicated Renografin. Apart from its well known negative inotropic properties, which are independent of the presence of the microbubbles produced by sonication, this agent causes marked myocardial hyperaemia which obviously affects any quantitative evaluation of perfusion.

Sonicated contrast agents

High-energy sonication allows the production of microbubbles small enough to pass through the capillaries. A piezoelectric crystal is the source of the controlled ultrasonic energy. The introduction of the tip of the sonicator horn into a solution results in the production of surface agitation and consequently microcavitation. A second generation of bubbles originates from the released cavitation gas bubbles. The stability of microbubbles obtained by sonication of a viscous carrier solution is probably related to the production of a 'shell' around the bubbles that protects them from coalescence. In general, however, the higher the carrier viscosity, the longer the bubble life and consequently the toxicity of the contrast agent.

The physics involved in microbubble generation and behaviour in in-vivo biological settings is complex. A series of factors, such as the viscosity, the surface tension and pH of the solution, affect size, concentration, decay and ultrasound backscatter of bubbles. Nowadays the most important aim is the production of microbubbles small enough to pass through the capillaries in order to prevent transient plugging of the microvasculature, this being one of the major causes of myocardial toxicity of contrast agents. Sonicated albumin has recently demonstrated physiological behaviour at the microcirculatory level and no adverse effects in humans. However, the ideal contrast medium is still to be developed. As yet, the identification of contrast-effective suspensions of stable and sufficiently small and uniform bubbles is the major purpose of current research in this field.

Contrast-enhanced image analysis

Quantitative analysis of contrast-enhanced images has been performed in both experimental and clinical settings. Myocardial enhancement in a specific region of interest immediately after contrast injection is related to regional myocardial blood flow and volume. The time-intensity curve of the myocardial gray level in one or more myocardial regions of interest can be easily obtained by using special video-intensitometric software. The intensity value of each pixel in a two-dimensional echocardiographic image is expressed as an absolute number, usually in an 8 bit grayscale (0-256), as gray levels or as a percentage of the maximal intensity obtainable. Intensity values of single pixels in a specified myocardial region of interest are averaged to obtain a mean spatial value, which is considered to be representative of the intensity value of the whole region of interest.

Time-intensity curves have a first phase during which a rapid increase of signal intensity occurs until a peak value is reached (wash-in phase). This is followed by a slow descending phase (wash-out phase). A number of parameters obtained by mathematical analysis of the time-intensity curve recorded in different flow conditions have been related to regional flow values. Although significant relationships have been found in some specific settings, no single parameter has been found of general applicability. Kaul et al. have demonstrated that in most flow conditions the time-intensity curves can be represented by gamma variate modelling and that the a-coefficient is strictly related to regional myocardial blood flow.

Regional intensity values are independently affected by many factors (input function, mean bubble size and their specific behaviour in coronary capillaries, technical...
Figure 1  Effect of coronary blood flow on videointensitometric curves. The changes induced by reduced regional coronary blood flow in videointensitometric curves obtained by myocardial contrast echocardiography are shown schematically. Upper panel: two different regions of interest (ROI) have been selected to determine the effect of coronary blood flow reduction on the assessment of the time-intensity curves. The image shows a short-axis view of the left ventricle obtained at the papillary muscle level in a patient in whom angiography showed a normal left circumflex artery and high grade stenosis of the left anterior descending artery. ROI 1 (in the vascular bed of the left circumflex artery) and ROI 2 (in the vascular bed of the left anterior descending artery) are positioned on a normally perfused and a hypoperfused segment, respectively. Lower panel: this figure shows an ideal study performed in a patient with a marked hypoperfused region. Time-intensity curves are obtained after intracoronary injection of a sonicated echo-contrast agent which acts as a myocardial flow tracer. They represent the time course of the mean spatial videointensity value change (%Δ of baseline videointensity) in each different ROI. In comparison with a normal videointensitometric curve (Normal CBF) the myocardial contrast echocardiography intensity curve obtained by a region of interest with reduced myocardial blood flow (Reduced CBF) shows a lower peak intensity value and a slower wash-out phase. Gamma variate modelling is used for the quantitative assessment of the time course of videointensity and the calculation of parameters of regional coronary blood flow in current settings. Adapted with permission [28]. □ = normal coronary blood flow; □ = reduced coronary blood flow.

characteristics of the individual patient imaging). Due to contrast agent variability and, to a lesser extent, to patient-to-patient variability of these factors, mathematical analysis of the time-intensity curves has not yet been extensively applied in a routine clinical setting [1291].

To date, quantitative determination of the extent of opacified and non-opacified myocardial areas as a percent of total myocardial area in a specific view (usually left ventricular short axis) seems to be the most practical and fruitful approach for the assessment of the extent of both risk area and post-reperfusion residual infarct area (whether in an experimental [30] or a clinical setting [15, 61] after an acute myocardial infarction). Villanueva et al. [31] have recently developed new echocardiographic software which performs the digital background subtraction of the baseline image (the pre-contrast image) from the post-injection image in a semi-automated mode, thus allowing increased differential display of perfused vs non-perfused areas. As a preliminary step in this procedure, the left ventricular images obtained at different stages of myocardial contrast echocardiography examination are automatically
importance for the accurate assessment of the extent of ability of multiple tomographic planes is of crucial, but avail-
can be accurately determined in this way
Cardiac at risk of necrosis if compared to technetium
Risk area. Furthermore, selective intracoronary injection
of left ventricular end-diastolic and/or left atrial pressure
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The assessment of reflow immediately after reperfusion, however, does not give very accurate infor-
various layers of the same vessel. The area is directly related to the final infarct size, which, moreover, is the major
determinant of functional damage of the left ventricle and consequent clinical outcome after acute myocardial
infarction. Evaluation of infarct size by haemodynamic parameters, which are an expression of overall left
ventricular function, is unreliable since, as demonstrated by Kaul et al., significant alterations in cardiac output
of left ventricular end-diastolic and/or left atrial pressure occur only if infarct size is greater than 25% of the entire
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infarction comprises not only the myocardial area with irreversible functional damage, but also the area that is
dysfunctioning, but still viable.
Myocardial contrast echocardiography has been shown to be a reliable method for identifying myocardium at risk of necrosis if compared to technetium
angiography. Left ventricular perfusion defects can be accurately determined in this way, but availability of multiple tomographic planes is of crucial importance for the accurate assessment of the extent of risk area. Furthermore, selective intracoronary injection
in both arteries gives a picture not only of antegrade blood flow, if still present, but also of the extent of intramyocardial collateral flow within the risk area.
Depending on the site of coronary injection of the contrast agent, the risk area may be defined as negative or positive. If the injection is proximal to the site of coronary occlusion or into the coronary artery, the area showing no contrast effect is considered the negative risk area. In experimental models, the cath-
eter may also be positioned just beyond the site of coronary occlusion with the injection of contrast medium defining contrast enhancement in the positive risk area. Kaul and co-workers demonstrated in canine experiments that the positive risk area is slightly, but significantly, larger than the negative one (4.98 ± 1.69 vs 3.97 ± 1.27 cm², P<0.01) and that the difference occurs in the epicardium.
There are several physical and physiological explanations for these observed differences: (a) lateral resolution artefacts inherent in all ultrasound systems produce expansion of the positive risk area and a corresponding diminution of the negative risk area; (b) blooming of the contrast signal can cause apparent encroachment of the negative contrast zone and expansion of the positive contrast zone; (c) pressure of contrast injection would result in a relative expansion of the positive risk area; (d) ischaemia-induced collateral vessels are more extensive in subepicardial layers; therefore, when the contrast medium is injected locally in the occluded vessel, it should travel farther outward radially in the epicardial surface by way of these collateral vessels, thus explaining the greater epicardial extent of the positive risk area.

**Clinical applications in myocardial infarction**

**Risk area and infarct size**

During acute myocardial infarction, immediately after coronary artery occlusion, the regional absence of flow delineates the risk area. This is, by definition, the myocardial area related to an occluded coronary artery, with complete absence of blood flow, either antegrade or collateral, and will probably undergo necrosis. This area varies greatly between individuals even in the presence of coronary occlusion occurring at comparable levels of the same vessel. The area is directly related to the final infarct size, which, moreover, is the major determinant of functional damage of the left ventricle and consequent clinical outcome after acute myocardial infarction. Evaluation of infarct size by haemodynamic parameters, which are an expression of overall left ventricular function, is unreliable since, as demonstrated by Kaul et al., significant alterations in cardiac output of left ventricular end-diastolic and/or left atrial pressure occur only if infarct size is greater than 25% of the entire left ventricle. On the other hand, regional wall motion abnormality analysis can lead to misleading results since the extent of wall motion alterations early after myocardial infarction comprises not only the myocardial area with irreversible functional damage, but also the area that is dysfunctioning, but still viable.

Myocardial contrast echocardiography has been shown to be a reliable method for identifying myocardium at risk of necrosis if compared to technetium angiography. Left ventricular perfusion defects can be accurately determined in this way, but availability of multiple tomographic planes is of crucial importance for the accurate assessment of the extent of risk area. Furthermore, selective intracoronary injection
...with improvement in regional myocardial contractile function after prolonged myocardial ischaemia followed by reperfusion is a fundamental prerequisite for myocardial viability[5,6,16,47,48]. In the absence of no reflow phenomenon regional left ventricular function, even if abnormal at rest and, therefore, indistinguishable from that of myocardium with no reflow, can considerably improve during low dose dobutamine infusion, because of the presence of myocardial viability and retained contractile reserve[47-49]. Myocardium with no reflow has no contractile reserve because of more extensive irreversible myocardial damage[47,48].

Therefore, no reflow phenomenon, as an expression of microcirculatory damage, is associated with relatively more extensive myocardial necrosis[49] and, as a consequence, is a predictor of poor regional and global contractile function[106]. On the other hand, microvascular integrity is an accurate indicator of adequate reflow shortly after coronary reperfusion and consequently of regional and overall functional recovery[5,6] in patients with acute myocardial infarction.

**Preconditioning effect**

Angina within 24 h before acute myocardial infarction seems to preserve coronary microcirculation and myocardial viability (thanks to a preconditioning effect), thus producing less evidence of no reflow phenomenon and consequently better preservation of regional function[106,107]. Because of this, ischaemic preconditioning limits myocardial infarct size after prolonged ischaemia. Villanueva et al.[107] tested the hypothesis that this reduction in infarct size is due to a preconditioning-induced limitation in the risk area. In an open-chest canine model, (preconditioning obtained with a 5 min occlusion of the left anterior descending coronary artery repeated four times prior to a 50 min coronary artery occlusion), they demonstrated, using serial myocardial contrast echocardiography, that preconditioning was capable of reducing the extent of risk area (31 ± 20% reduction). The preconditioning-induced reduction in risk area size seems to be due to increasing flow at the lateral borders of its bed.

**Infarct-related artery patency, microvascular integrity and myocardial function**

Presence–absence of myocardial contrast echocardiography enhancement in post-acute myocardial infarction myocardium indicates integrity–destruction of microcirculation, respectively. However, presence–absence of myocardial contrast echocardiography enhancement, as demonstrated by Ito et al.[106] is independent of infarct-related artery patency. In a series of 11 patients studied in our laboratory we observed myocardial contrast enhancement in 14 out of 14 post-infarction dysfunctioning segments with occluded infarct-related artery (blood supply to viable myocardium was ensured...
by collateral coronary circulation) and only in nine out of 20 segments related to a patent infarct-related artery (even if the infarct-related artery was reopened adequate perfusion was not re-established[52]).

Microvascular integrity, moreover, is an indicator of viability. In a series of 39 patients with acute anterior myocardial infarction studied by Ito et al[16], those with no reflow (nine patients), if compared to those with absence of no reflow phenomenon (30 patients), had a worse average segmental score and lower left ventricular ejection fraction (0.97 ± 0.36 vs 0.44 ± 0.41, P<0.01; and 42.7 ± 8.9% vs 56.4 ± 13.4%, P<0.05 respectively) 1 month after acute myocardial infarction. Similarly, Sabia et al[6] demonstrated that in patients with recent myocardial infarction and a totally occluded infarct-related artery, functional recovery (decrease in wall motion score index, increase in ejection fraction) at 1 month following infarct-related artery reopening by PTCA was observed in patients with collateral flow as shown by contrast enhancement of myocardium (obtained by injecting at the time of coronary angiography contrast in the non-infarct related coronary artery), but not in those without contrast enhancement.

Recent observations in our laboratory have also shown that myocardial contract echocardiography-enhanced post-myocardial infarction dysfunctioning segments are more likely to improve the motion in response to dobutamine infusion[63]. These semiquantitative observations have been confirmed by quantitative evaluations (myocardial thickening evaluated by omni-plane transoesophageal echocardiography)[67]: in a series of 13 patients with recent myocardial infarction, 40 segments were dysfunctional within the infarct area. Among these segments, those with contrast enhancement at myocardial contrast echocardiography significantly increased their thickening during low dose dobutamine infusion (from 20.2 ± 11.8% to 28.7 ± 14.8%, P<0.0001) as compared to dysfunctional and non-opacified echocardiography-enhanced segments in which thickening did not increase (from 7.7 ± 12.5% to 12.4 ± 16.6%, P=ns). Therefore, microvascular integrity after acute myocardial infarction guarantees a certain degree of baseline regional function and contractile reserve and myocardial contrast echocardiography is able to identify myocardium with preserved microvasculature and a strong likelihood of viability.

Myocardial contrast echocardiography has recently been used to assess the presence and extent of the functional border zone[54-57], which is defined as the presence of non-ischaemic regional dysfunction at the lateral borders of damaged or ischaemic myocardium. This concept, pioneered by Gallagher et al[55], was applied to echocardiography by Buda et al[56,57]. Nanto et al[54] demonstrated the presence of the functional border zone in patients by performing a simultaneous analysis of myocardial perfusion and wall motion abnormalities: the size of this area was determined by measuring the length of the endocardium that showed asynergy in the echo-enhanced (non-ischaemic) area.

Assessment of collateralized myocardium

In the acute phase of myocardial infarction, the relative amount of infarcted and viable myocardium within the risk area depends on the duration of coronary occlusion and on the extent of collateral blood flow[1,42]. In fact, when a coronary artery is occluded, its perfusion bed can be at risk of necrosis; however, a previously developed, but collapsed collateral circulation can be opened from an increased driving pressure due to the fact that infarct-related artery pressure is very low because of this sudden occlusion. Post-ischaemic, but collateralized myocardium, thanks to preserved microvascular integrity, can remain viable for a long time.

Myocardial contrast echocardiography is accurate in mapping the extent of collateralized myocardium[58,59] (Fig. 2), which is, by definition, the territory with double possible perfusion (either anterograde or coming from a different donor artery). So, if the native coronary artery is occluded, the injection of sonicated contrast medium in the other artery can show myocardial opacification in segments within the occluded artery perfusion bed. If the native coronary artery is reopened, the real extent of its perfusion bed can then be estimated with infarct-related artery contrast injection (myocardial contrast echocardiography opacified area). The myocardium that is opacified by injections both in the infarct-related artery and in the other coronary arteries is the collateralized one.

As recently demonstrated by Sabia et al[6], the percent of the occluded bed supplied by collaterals, defined by myocardial contrast echocardiography, correlates poorly with the angiographic collateral grade, and functional recovery is better in patients with more than 50% of the occluded bed collateralized. This means that myocardial contrast echocardiography is more accurate than angiography in the evaluation of presence and extent of functionally effective intramyocardial collateral circulation.

Microvascular reserve

In the presence of epicardial coronary artery stenosis, coronary flow reserve can be impaired and the degree of impairment be used to assess the physiological significance of the stenosis[60]. However, even in the absence of epicardial lesions, coronary reserve can be abnormal because of functional or structural alterations involving the microvascular network[61].

Transient myocardial ischaemia, sufficiently brief to avoid cellular and vascular necrosis (15 min), has been demonstrated by Nicklas and Girs to decrease coronary flow reserve[62], postulated several hypotheses for this finding: increased arteriolar or capillary vascular resistance secondary to local interstitial oedema or to neutrophil plugging; altered vascular reactivity by way of the sympathetic nervous system or through endothelial dysfunction with loss of endothelial mediated vasodilation. Therefore, after prolonged myocardial
ischaemia, even in the absence of epicardial coronary stenosis and in the presence of anatomical integrity of the intramyocardial vascular network, microvasculature can be functionally altered, with reduced vasodilating reserve decreasing its resistance to flow under administration of vasodilating drugs. This behaviour has been observed in experimental studies and is considered to be a sort of ‘vasculature stunning’ \[1621\] or ‘damage’ that renders the microvasculature capable of supplying an amount of blood flow sufficient only for baseline conditions but which cannot be increased in conditions requiring flow increment for proper function.

In non-infarcted collateralized myocardium, even if myocardial blood flow is normal at rest, microvascular reserve can be impaired. In five patients with an occluded coronary artery, but without myocardial infarction, studied by positron emission tomography McFalls et al.\[631\] found a significant reduction in absolute coronary flow reserve in collateralized regions when compared to the control region (dipyridamole myocardial blood flow/resting myocardial blood flow was 1.9 ± 1.0 in collateralized regions vs 4.1 ± 0.8 in control regions \[P<0.01\]).

Myocardial contrast echocardiography has the potential to assess functional alterations of the microvasculature. Intracoronary injection of echocontrast administered while an intravenous vasodilatory agent is being given can show considerable increase in signal intensity and in area under the time-intensity curves in normal myocardial segments secondary to augmented

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**Figure 2** Collateral-dependent myocardium. This is an example of collateral-dependent myocardium in a patient with an occluded right coronary artery. The (a) panel shows the baseline short-axis of the left ventricle at the papillary muscle level and the (b) panel shows the same view after injection of sonicated ioxaglate in the left coronary artery: the myocardial opacification has been obtained both in left and right coronary perfusion beds, thus indicating the presence of an extensive collateralization of the right coronary artery from the left coronary artery. Both images have been selected in end-diastole using digital cine-loop frame by frame reviewing.
flow in these areas, while a relatively reduced increase in these two parameters has been observed in the myocardial area with impaired coronary reserve\cite{66}. In fact, coronary vasodilators (such as adenosine, dipyridamole, dobutamine, papaverine) are able to induce an increase in myocardial intravascular volume, as a result of dilatation of coronary microvessels as well as recruitment of previously collapsed capillaries. However, the experience with these procedures is limited and their safety in the very acute phase of myocardial infarction is as yet unassessed.

**Limitation of myocardial contrast echocardiography**

Although very promising as a research and clinical tool, myocardial contrast echocardiography presents, nowadays, some important limitations, knowledge of which should not be ignored: (1) at present, achievement of quantitation of coronary flow is incomplete, due to the non-uniformity and instability of clinically available microbubbles: thus, functional assessment of coronary artery disease in patients is limited to a qualitative approach; (2) limited data are available as regards reproducibility of myocardial contrast echocardiography, an important issue for clinical studies, especially multicentre ones: important sources of variation in the intensity-perfusion relationship are contrast agent characteristics and, to a lesser extent, patient-to-patient variability; (3) the safety issue has not been adequately addressed and available evidence of safety comes from a limited number of clinical studies\cite{66}.

**Conclusion**

Great progress has been made in the management of patients with acute myocardial infarction in the last decade. Considerable results have been achieved not only in the management of functional consequences of the disease, but also, and more importantly, in the attempts to reduce irreversible damage (evolution to scar) of myocardium undergoing prolonged and severe ischaemia because of acute reduction of blood supply. This important result is obtained by restoring flow as soon as possible, or if this is delayed, re-establishing definitive infarct-related artery patency later.

In order to maximize the use of all the therapeutic procedures available to achieve these results it is important to know more about the functional potential recovery of the dysfunctioning myocardium whose infarct-related artery will be reopened early or late after myocardial infarction. This potential seems to be mainly due to the existence of microvasculature integrity and to its ability in providing blood to a dysfunctioning, but still viable, myocardium.

Myocardial contrast echocardiography has the potential to identify such a condition since it allows: (1) evaluation of microvasculature flow conditions after infarct-related artery reopening and therefore the identification of no reflow phenomenon; (2) comprehension of coronary anatomy and myocardial perfusion relationships and, consequently, identification of the coronary artery supplying blood flow to the dysfunctioning myocardium; (3) immediate identification of the reflow effect of coronary angioplasty in an occluded infarct-related artery by observing echocontrast opacification of myocardium after its injection in the reopened infarct-related artery. One major limitation of this attractive technique is the need to perform cardiac catheterization to inject echocontrast into the coronary arteries. However, recent animal studies\cite{33} have shown promising results after the administration of contrast injection into the right atrium, provided that accurate digital evaluation systems are used and vasodilating agents (dipyridamole, adenosin) employed. By producing maximal vasodilatation these agents increase echocontrast concentration in the myocardium thus enhancing its reflectivity to the ultrasound beam, which can then be detected by echocardiographic examination.

Research is currently being done to fully explore the potential of new contrast agents which pass the pulmonary bed after intravenous injection, but are still capable of opacifying cardiac cavities, reaching coronary arteries and improving the Doppler signal\cite{66}. At the same time some aspects of ultrasound physics are also being explored, including the second harmonics application that theoretically can improve echocontrast detection during echocardiographic imaging\cite{67,68}. If all these efforts are successful, myocardial contrast echocardiography may be performed serially and intravenously in acute and subacute phases of myocardial infarction thus obtaining not only unique information on the evolution of risk area and infarct size and the effect of reperfusion on them, but also on the presence of reflow or no reflow after infarct-related artery reopening. All these aspects are of great pathophysiological interest, and have enormous clinical and prognostic implications.

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