

# Added value of contrast echocardiography in assessing myocardial viability

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Although echocardiography has a well established role in the evaluation of patients with coronary artery disease, in many cases it does not provide appropriate information regarding the processes underlying ventricular wall motion abnormalities. In conditions like acute ischaemia, stunning, hibernation, infarction, and the no reflow phenomenon, improved diagnostic information might be derived from myocardial perfusion data. In recent years, satisfactory results at the identification of myocardial perfusion abnormalities have been achieved using hand agitated or sonicated radiographic contrast agents directly injected into the coronary arteries during cardiac catheterisation.<sup>1-12</sup> Subsequently, it became apparent that accurate and reproducible myocardial enhancements were attainable by peripheral venous injection of second generation contrast agents<sup>13-17</sup> and harmonic intermittent imaging,<sup>18-22</sup> whose sensitivity in detecting microbubbles was further increased by the introduction of power Doppler.<sup>23, 24</sup> This non-invasive, non-nuclear approach to the study of myocardial perfusion has expanded the interest of cardiologists in myocardial contrast echocardiography.

The capability of contrast echocardiography to recognise the presence of viable myocardium is based on the assumption that preserved microvascular integrity, as seen by intracoronary contrast administration, is a necessary prerequisite of viability in patients with recent or remote myocardial infarction.<sup>4-6</sup> However, there is some debate over the recognition of viable tissue from the perfusion data. In the studies in which the recovery of myocardial function was considered as the gold standard of viability, some discrepancies were noted concerning the reliability of contrast echocardiography in predicting regional recovery. In patients who suffered from an acute myocardial infarction, the specificity of the technique in recognising viable tissue was only 18% early after the onset of symptoms,<sup>9</sup> but was 57-67% in the chronic phase.<sup>10, 11</sup> Another controversy concerned the conflicting results obtained in the prediction of recovery of global versus regional left ventricular function based upon contrast echocardiographic evidence of viable myocardium. Therefore, it is likely that more tailored approaches to the use of contrast echocardiography in different clinical settings may be valuable in providing reliable information on myocardial viability. In order to overcome these limitations and to maximise its contribution, this review focuses on the additional value of myocardial contrast echocardiography in the study of viable myocardium.

## Early echo contrast in acute myocardial infarction

Neither the patency nor the severity of coronary stenosis of the infarct related artery indicates the extent of microvascular integrity. Although prominent information may be provided by single photon emission computed tomography (SPECT) to assess the extent of salvaged myocardium, and to predict late functional recovery in patients with acute myocardial infarction,<sup>25</sup> limited availability prevented widespread use of this nuclear approach. In those patients admitted to coronary care units, the use of intravenous contrast agents peripherally injected may be the only method to provide data on myocardial microvasculature. In the early hours of infarction, the patterns of myocardial perfusion following intracoronary administration may be different depending on whether the contrast agent was administered during acute coronary occlusion or after reperfusion.<sup>1, 3, 7, 9</sup> During occlusion, the lack of opacification in the downstream non-perfused myocardium may be clearly outlined by contrast echocardiography (fig 1, left panel). In this condition, the detection of an impaired regional function by two dimensional echocardiography provides only indirect assessments and tends to overestimate the entity of the jeopardised myocardium.<sup>26</sup> Conversely, in experimental studies the identification of the perfusion defect by contrast echocardiography guarantees a direct and more accurate quantification of the area at risk for necrosis.<sup>27</sup> Furthermore, since a compromised global systolic function is apparent only if the perfusion defect is relevant, the echocardiographic assessment of left ventricular ejection fraction might not reflect the occurrence of a jeopardised dysfunctional myocardium unless the damaged tissue reaches a relevant extent.<sup>27</sup>

In experimental studies, when the contrast agent is administered shortly after reperfusion is achieved, contrast echocardiography may allow us not only to distinguish between successful and failed reperfusion,<sup>17, 28</sup> but it may also provide additional information on the state of the coronary microcirculation. In this respect, the degree of myocardial enhancement depends on epicardial and microvascular coronary haemodynamics. In case of rapid coronary reopening, and in the absence of residual vessel narrowing, a downstream brighter contrast effect caused by reactive hyperaemia is visible as opposed to the surrounding myocardium (fig 2). Conversely, if a flow limiting stenosis is still in existence or if the agent is administered after reactive hyperaemia, no significant differences in the opacification of the

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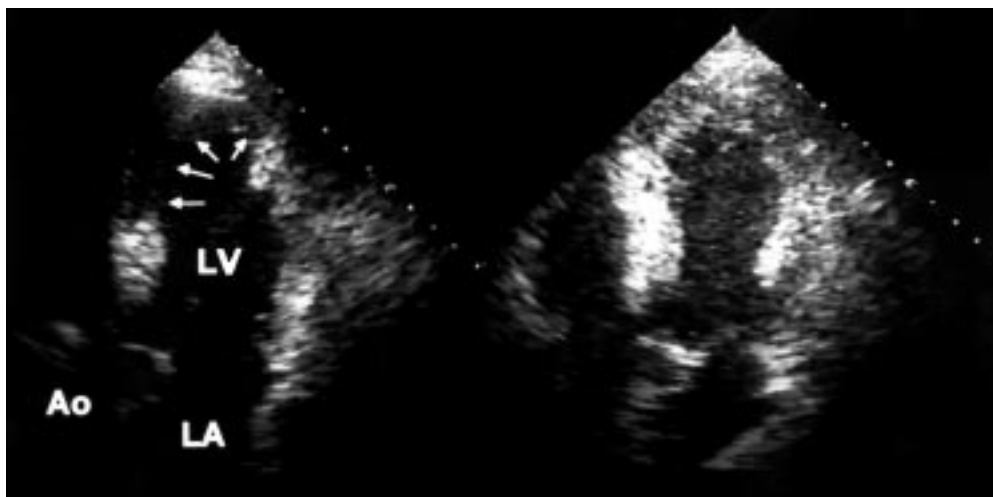


Figure 1 Left panel shows myocardial risk area (arrows) delineated by contrast injection into the left coronary artery in a patient with acute infarction caused by a total occlusion of the left anterior descending artery. The right panel illustrates a low reflow state after angiographically successful primary PTCA in the same patient.

reperfused myocardium in the two regions are generally apparent (fig 3). Despite the achievement of adequate coronary recanalisation at angiography, trivial or absent enhancements in the downstream myocardium proved to be associated with no or low reflow.<sup>1 3 7 9</sup> (fig 1, right panel). Hence, the images obtained by myocardial contrast enhancement may be highly explicative of the presence of this perfusion defect. The occurrence of no reflow was reported in 18–25% of patients admitted to the coronary care unit with a significant ST segment elevation undergoing myocardial contrast studies before and after primary percutaneous transluminal coronary angioplasty (PTCA). In this scenario the added value of contrast echocardiography is that a TIMI 3 flow in the culprit vessel (which is considered the marker of successful reperfusion from the angiographic standpoint) was seen in all the patients following PTCA.

The possibility of stratifying patients according to their myocardial perfusion pattern may introduce a useful non-invasive counterpart of that based on TIMI flow coronary angio-

graphic assessment. It has been acknowledged that the estimates of coronary flow shortly after thrombolysis or primary PTCA do not always correlate with tissue perfusion. While no myocardial opacification can be visualised in TIMI 0 and 1 as a result of failed reperfusion, a more circumscribed perfusion defect caused by no reflow is manifest in all TIMI 2 patients and in about one third of those with TIMI 3 flow.<sup>29</sup> Since significant left ventricular function recovery was observed only in patients with TIMI 3 flow and adequate myocardial opacification of the downstream territory, we may assume that the accomplishment of satisfactory myocardial opacification is a necessary requirement of subsequent recovery, regardless of the information provided by the angiographic data. Therefore, it seems conceivable that a patient categorisation based on TIMI flow grading and perfusion data may improve the prognostic significance of the angiographic assessment.

The major contributions of contrast echocardiography to the viability assessment in acute myocardial infarction derives from its capability to predict early the late global ventricular recovery as well as clinical outcome from perfusion imaging. As far as the clinical studies accomplished shortly after revascularisation are regarded, intracoronary contrast

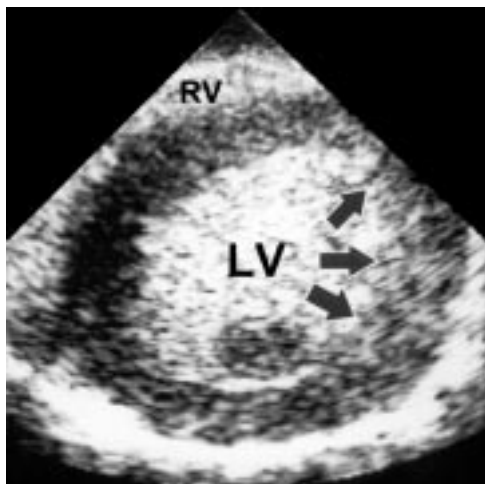


Figure 2 Increased contrast effect in a myocardial area (arrows) following the release of coronary occlusion in an experimental animal model. The contrast agent was injected intravenously during reactive hyperaemia.

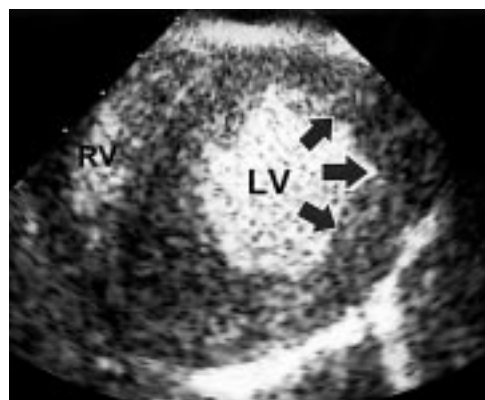


Figure 3 Homogenous myocardial contrast effect after the release of coronary occlusion in the absence of reactive hyperaemia in the dog heart.

echocardiography had proved to be remarkably accurate at identifying patients who subsequently recovered their global left ventricular function. Furthermore, the detection of circumscribed perfusion defects pertinent to no reflow were revealed to be associated with late and incomplete recovery.<sup>1 3 7 9</sup> The clinical implications of these findings are the result of the close correspondence between contrast enhancement and outcome. Indeed, adequate contrast opacification at the time of the study corresponded to a better clinical course during the subsequent follow up, whereas more raised frequencies of cardiac events, from arrhythmia to pericardial effusion and congestive heart failure, were reported in those with no reflow.<sup>30</sup> In a recent study, myocardial opacification in the risk area after an acute myocardial infarction was used to predict both short and intermediate term prognoses. The number of events (cardiac death, non-fatal myocardial infarction, and repeat admission) during a 22 month follow up was higher in patients with appreciable myocardial contrast enhancement as opposed to those not exhibiting acceptable myocardial visualisation.<sup>31</sup>

#### **Myocardial echo contrast at hospital discharge for acute infarction**

The clinical utility of contrast echocardiography is ascertainable not only in studies carried out in the early phase of infarction, but also by those performed later in the clinical course of the disease. The usefulness of the late assessment of tissue perfusion after infarction seems to be related to better understanding of the mechanisms responsible for left ventricular dysfunction, which may be extrapolated from myocardial contrast enhancement at this stage. Accordingly, the lack of myocardial opacification is attributable to the absence of viability, while adequate visualisation of myocardial tissue may reflect preserved microvascular integrity, which is a marker of myocardial viability.

The relation between intracoronary myocardial contrast enhancement performed at hospital discharge, and recovery of left ventricular function were evaluated in patients with first acute myocardial infarction and a patent infarct related artery after three to six months.<sup>5 12</sup> The results of these studies showed that the improvement in left ventricular performance might be anticipated by examining cardiac tissue perfusion at the time of discharge. A late ventricular recovery was observed in most of the patients in whom an intact coronary microcirculation was present in the infarct area, while that was not the case in those exhibiting perfusion abnormalities involving more than 50% of the dysfunctional myocardium, despite a patent culprit artery. It was, therefore, evident that the recognition of microvascular integrity at the time of hospital discharge permits us to foresee subsequent left ventricular recovery, which suggests myocardial stunning as one of the mechanisms responsible for the impaired ventricular function.

#### **Perfusion studies in chronic ischaemic heart disease**

The identification of viable myocardium in the setting of chronic ischaemic heart disease has important prognostic and treatment implications. In this regard, the use of contrast echocardiography has been mainly focused on the identification of microvascular integrity in regions of chronic dysfunctional myocardium. Based on intracoronary perfusion imaging, different authors recognised the possibility of identifying regions of dysfunctional myocardium able to improve after coronary revascularisation with PTCA or coronary artery bypass grafting.<sup>8 10 11</sup> Hence, microvascular integrity as detected by the contrast enhancement in dysfunctional segments may provide additional useful information that is complementary to those derived from the determination of the inotropic reserve with dobutamine echocardiography.

In chronic ischaemic heart disease, clinical research studies have been designed to identify methods that best predict recovery of function based on indices of capillary density. Despite good sensitivity (ranging from 80–95%), the specificity of myocardial echo contrast was lower than dobutamine echocardiography (50–75% *v* 85%). Similar accuracy in the identification of segments that subsequently improved was documented in other studies in which patients were treated either medically or by coronary revascularisation.<sup>4 7</sup> In the latter, adequate opacifications of myocardial regions had an almost 50% probability of matching with their subsequent recovery, while the detection of lower capillary density corresponded less often with their improvement. Therefore, as in those with acute myocardial infarction, in patients with chronic ischaemic heart disease a preserved microvascular integrity—demonstrated by contrast enhancement—appears to be essential but not sufficient to maintain tissue viability. It is conceivable that the lack of recovery in areas of normal or near normal perfusion is caused by extensive fibrosis in the subendocardium following non-transmural infarction or by the presence of widespread areas of scattered fibrosis within the myocardium which are large enough to prevent their subsequent improvement.<sup>32</sup> In patients with a prior myocardial infarction, the possibility of obtaining accurate and reliable data on viability by this technique has been recently documented by comparing the effects of contrast agents, injected peripherally<sup>22</sup> or intracoronary,<sup>33</sup> with those elicited in myocardial perfusion scintigraphy studies.

#### **Advantages and limitations of contrast echocardiography in viability assessment**

A number of technical and physical limitations of myocardial contrast echocardiography affecting both accuracy and feasibility should be taken into consideration. Compared to SPECT, the accuracy of myocardial echo contrast echocardiography following intravenous administration in detecting perfusion defects is still limited, implying its low sensitivity in routine clinical practice.<sup>34</sup> Indeed, the information

provided by the technique may be restrained either by the occurrence of artefacts (for example, contrast induced signal attenuation, saturation, and "blooming" or the spatial heterogeneity of contrast intensity),<sup>35</sup> or by the imaging modalities which have been used. Therefore, critical importance should be conferred on the use of adequate power and appropriate gain setting as well as on advances in instrumentation for bubble technology (that is, harmonic intermittent imaging and power Doppler).<sup>18-24</sup> Additionally, appropriate dosages and optimal concentrations of contrast agents are still to be defined for the most part. Finally, although an adequate quantification of tissue imaging is highly desirable, only semi-quantitative assessment of myocardial perfusion is currently available.

However, several factors are in favour of the use of myocardial echo enhancement of tissue perfusion. The expanding availability of echocardiography scanners in local and community hospitals in most of the industrialised countries is an important element. For clinical cardiologists, the repeatability of the procedure may allow us to follow the early stages of acute ischaemic syndromes and to evaluate the effects of treatment. Early non-invasive assessment of myocardial reperfusion might be important to identify rapidly high risk patients and to select candidates for adjunctive treatment, including rescue PTCA. The assessment of myocardial microvasculature after thrombolytic treatments or PTCA procedures appears to be a highly promising approach in order to establish treatments of the no reflow phenomenon.<sup>36</sup> In chronic ischaemic heart disease, these techniques seem well suited for use as a complementary tool, rather than as an alternative to two dimensional and stress echocardiography. As opposed to nuclear scanners, contrast echocardiography allows the operator to achieve a higher spatial and temporal resolution, which may lead to more accurate information on myocardial perfusion. In addition, although contrast agents have not yet been approved by the regulatory authorities for myocardial tissue perfusion, a large number of experimental and phase I-III clinical studies support their safety.

As far as new trends are concerned, a better detection of contrast microbubbles in myocardial tissue and the validation of quantitative approaches to the evaluation of tissue perfusion are two of the forthcoming major developments of contrast echocardiography.<sup>37</sup> Finally, the integrating contributions of two dimensional, stress, and contrast echocardiography<sup>38-40</sup> may be particularly advantageous in improving the specificity of the technique by combining the evaluations of cardiac anatomy, regional and global ventricular function, contractile reserve, and microvascular integrity.

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