Editorial

Myocardial Contrast Echocardiography in the Evaluation of Myocardial Viability

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During the last twenty years, progress in cardiovascular surgery and interventional cardiology, along with an ever improving diagnostic armory, have led to a marked increase in interventions aimed at reperfusing ischemic myocardial territories. However, the initial concept of ischemia in clinical practice encompassed only epicardial vessels. Since the clinical objective is improved function, which is also dependent on the status of the microvasculature and myocyte integrity of the ischemic area, there was a gap to be filled between reperfusion and functional recovery. In the mid 1970s, it was observed that even akinetic segments could recover their function following revascularization in some cases,[1,2] which led to the concepts of "stunned" and "hibernating" myocardium.[3,4]

In current clinical practice, there is an obvious need to discriminate between patients who are going to benefit from an intervention and those who are not likely to, by determining whether a dysfunctional myocardial wall region will recover its function after reperfusion, i.e. whether this region is viable. It has been demonstrated that lack of viability indicates low possibility for functional improvement after revascularization.[5,6] Consequently, the incorporation of viability assessment into the process of decision-making regarding reperfusion may help in avoiding unnecessary procedures and the entailed risk.[7] In addition, the evaluation of viability is a powerful predictor of the outcome for survivors of ST elevation acute myocardial infarction (STEMI), conferring incremental prognostic information.[8]

Echocardiography is a highly suitable method for the noninvasive assessment of cardiac structure and function. With the advent of contrast media and the evolution of hardware/software packages enabling cardiologists to assess myocardial perfusion with myocardial contrast echocardiography (MCE), it is now possible to evaluate the microvascular integrity of a region and thus predict its potential for functional recovery.

Basics of contrast echocardiography

The study of myocardial perfusion with echocardiography involves an intravascular injection of contrast agents that can scatter ultrasound.[9] The newer ultrasound contrast agents are microbubbles that resonate when excited by diagnostic ultrasound frequencies, producing an increasing ultrasound backscatter from the blood. These microbubbles are rheologically similar to erythrocytes.[10] One of the major advances in contrast echocardiography is the capability of contrast agents to be stable enough to pass the pulmonary circulation and to concentrate in different regions of the myocardium, reflecting the relative myocardial blood

volume within the myocardial microvasculature. It is known that more than 90% of intramyocardial blood volume is within the capillary compartment. Special techniques use the interaction between ultrasound and microbubbles of contrast agents to permit the amplification of the echo signal to noise ratio.[11]

Current refinements, not only in microbubble engineering but also in the instrumentation for their detection, are primarily responsible for the improvement in contrast echocardiography. Ultrasound imaging techniques have been modified to optimize microbubble detection in both the left ventricular cavity and the myocardium. Furthermore, as new imaging techniques allow real-time perfusion imaging (instead of intermittent imaging with the initially used triggering techniques), it has become possible to assess wall motion and perfusion simultaneously, thus enabling the concurrent evaluation of contractile reserve and microvascular integrity, the two significant correlates of viability.

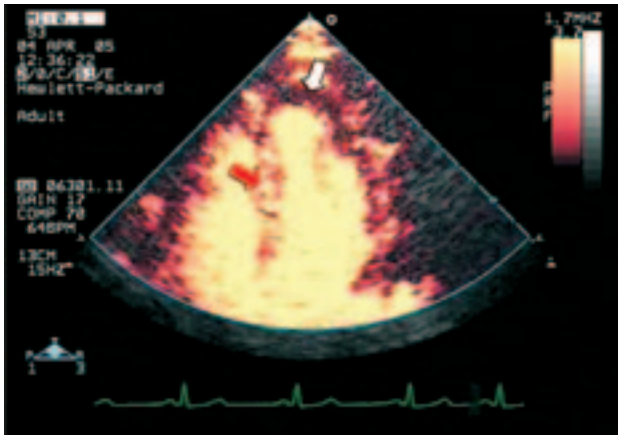

Figure 1. Myocardial contrast echocardiography study at rest. Example of no-reflow in a patient with ST elevation acute myocardial infarction, following primary percutaneous coronary intervention to a lesion in the mid-left anterior descending artery. The area of absence of myocardial enhancement in the apex is evident (white arrow), as opposed to the interventricular septum which is opacified (red arrow).

Assessment of myocardial viability

Detection of myocardial viability in acute coronary syndrome

Primary coronary angioplasty and thrombolysis are widely used in patients with evolving STEMI. Unfortunately, many patients are left with significant residual left ventricular dysfunction. The differentiation between stunned and necrotic myocardium may aid in risk stratification, identifying patients at increased risk of congestive heart failure, ventricular tachycardia and death. The early detection of epicardial coronary patency after thrombolysis or angioplasty is a determining factor for the restriction of the infarct size. Restoration of epicardial coronary artery patency is not equivalent to restoration of nutritive tissue flow.[12] Functional and structural microvascular disturbance is an important pathophysiologic phenomenon in the setting of reperfused STEMI. The microvascular integrity in the infarct area is a necessary requirement for the salvage of the myocardium, and it depends on the duration of the ischemic period and on the collateral flow in the region. MCE principally interrogates the intramyocardial microvasculature; it is thus ideally suited for assessing microvascular reflow after acute infarct reperfusion. Myocardial regions of microvascular volume loss or hypoperfusion appear as contrast distribution defects (Figure 1).[13,14] When collateral circulation has developed, contrast enhancement varies depending on the extent of the collateral circulation.[15]

Early studies using intracoronary MCE and subsequent ones involving the intravenous injection of contrast agents have demonstrated that this method is useful in assessing reperfusion, manifested as contrast enhancement in the area at risk.[12,14,16] The presence of adequate contrast enhancement has been shown to be a marker of viable myocardium**.** Since reperfusion cannot be accurately assessed on clinical grounds, a rapid bedside test using MCE is useful for identifying patients with failed reperfusion, who might be candidates for additional therapy such as rescue angioplasty. Many investigators have shown that patients with adequate contrast opacification in the infarct area demonstrate better ventricular function compared with patients who have permanent defects.[15,16] Conversely, if the coronary artery occlusion is still in existence, the size of the perfusion defect delineates the area at risk, according to Coggins et al.[17] Repeating MCE shortly after reperfusion and comparing the defects that appear provides a simultaneous assessment of both myocardial microcirculation and the success of the therapeutic intervention.[18] Sakuma et al[19] showed that the most suitable time for performing MCE in order to predict early ventricular functional recovery is on the second day following reperfusion. In addition, Rovai et al[20] demonstrated that increased contrast enhancement in the infarct area following reperfusion, at a time when reactive hyperemia has subsided, reflects preserved microvascular integrity. Delayed opacification in the infarct area with triggering

imaging is an important marker of regional recovery,[21] regardless of the severity of residual stenosis in the infarct related artery. Senior et al[22] showed that contrast opacification may be seen in segments unresponsive to dobutamine, and this could predict recovery of myocardial function. Interestingly, more and more studies emphasize the important role of MCE in delineating the functional area at risk in patients with STEMI. Partial opacification within the infarct area was seen in most patients with TIMI flow grade 2 after successful reopening of the infarct-related artery and in one out of three patients with TIMI flow grade 3 because of the low or no-reflow phenomenon.[16] Among patients with TIMI flow grade 3 significant improvement in ventricular function and better prognosis during follow-up was observed only in patients who had adequate contrast opacification within the risk area. These findings were also confirmed by Stone et al[23] in a more recent study. The authors concluded that satisfactory opacification within the infarct area is essential for its recovery, regardless of the information provided by the angiographic data. According to Lepper et al,[15] patients without the no-reflow phenomenon, as demonstrated by the evaluation of myocardial perfusion with MCE, had better coronary flow reserve 24 hours after angioplasty as well as an improvement in ventricular function one month later, compared to those with no-reflow. In this group of patients, MCE is far superior to the other forms of reperfusion assessment, such as ST segment resolution, corrected TIMI frame count or myocardial blush grade. The latter two methods assess the degree of reflow or no-reflow phenomenon angiographically. According to a study by Greaves et al,[24] neither corrected TIMI frame count nor myocardial blush grade showed any significant relation with the follow up assessment of regional wall motion systolic index. Therefore, MCE is a method of choice to assess myocardial perfusion status.

Widening the prognostic scope, Ito et al[25] looked into the clinical implications of the no-reflow phenomenon using intracoronary MCE and demonstrated that patients with no opacification within the infarct area were more likely to present congestive heart failure and pericardial effusions early after myocardial infarction.

Many studies have shown that the sensitivity of MCE in predicting recovery of function after reperfusion varies from 62% to 96%, with low to moderate specificity (18-67%).[19,26-28] It is significant that Main et al[27] reported that 90% of perfused myocardial segments improved after revascularization in the post-MI period, whereas most of the segments without perfusion remained unchanged. Balcells et al[29] showed that the presence of perfusion on MCE, from either collateral or antegrade flow in patients with STEMI before a primary coronary intervention, predicts the maintenance of perfusion and recovery of systolic function, while a perfusion defect on MCE performed early after the intervention predicts the presence of severe hypokinesis or akinesis at four weeks post-MI with a sensitivity of 95%. Conversely, 90% of the segments with normal perfusion early after the coronary intervention were normokinetic or mildly hypokinetic four weeks later. Similarly, Janardhanan et al[30] demonstrated that homogeneous opacification on MCE predicted recovery in approximately 85% of the studied myocardial segments. Recently, the same group[31] presented for the first time the utility of intravenous MCE, quantitatively and qualitatively, in detecting collateral blood flow early after acute myocardial infarction.

In several studies MCE compared favorably with dobutamine stress echocardiography in predicting regional left ventricular dysfunction after acute myocardial infarction.[9,26,28] Both modalities have been used independently to detect the presence of myocardial viability in this group of patients. Nowadays, many investigators[15-31] believe that the gold standard of defining viability is the recovery of myocardial function after revascularization, meaning that the presence of minimal islands of viable myocardium has no prognostic value. It is known that viability within a segment of myocardium is not an all-or-nothing phenomenon, while viable cells may coexist with necrotic myocytes. There is extensive evidence that functional recovery is dependent on the degree of myocyte loss and the extent to which they are replaced by fibrous tissue.

Despite these concerns, many efforts aimed at evaluating the microvasculature are likely to gain increasing importance in the clinical arena, defining the precise role of MCE in the prognosis of patients with coronary artery disease. Over the years, a variety of viability techniques have been developed. These techniques are able to predict not only improvement of function, but also improvement in exercise capacity and reserve left ventricular remodeling, as well as contributing to long-term prognosis. Furthermore, MCE is more sensitive than the currently used electrocardiographic and troponin I criteria, and evaluation of myocardial per-

fusion defect by MCE complements regional wall motion abnormality assessment by conventional echocardiography for accurate diagnosis of acute coronary syndrome without ST elevation.

Detection of viable myocardium in chronic coronary artery disease

Heart failure has significant mortality, morbidity and cost complications. A recent meta-analysis has shown that the beneficial effect of revascularization on heart failure applies only in patients with hibernating myocardium. Myocardial hibernation has been recognized as a mechanism of functional down-regulation, employed by the "smart heart" in order to preserve myocardial tissue integrity through lowering of its energy requirements.[4] Hibernating myocardium exhibits impaired systolic function at rest, but the restoration of coronary flow leads to recovery of its contractility.[33] Therefore, hibernating myocardium is viable myocardium and its detection in patients with ischemic cardiac disease is crucial. Only a few studies have evaluated the role of MCE in identifying hibernating myocardium, because of the many technical difficulties. Early studies[34,35] have shown the effectiveness of intracoronary MCE in detecting hibernating myocardium. Intracoronary MCE has high sensitivity but low specificity in predicting recovery of myocardial function after reperfusion in patients with left ventricular ischemic dysfunction. Interestingly, in the EchoLab, Aggeli et al[36] reported that harmonic power Doppler imaging had similar accuracy (74%) to dobutamine stress test (79%) in predicting functional myocardial recovery after coronary bypass surgery in patients with depressed left ventricular function. Moreover, Shimoni et al[37] found that the diagnostic accuracy of MCE increased when a quantitative method of myocardial perfusion was used. Another interesting report comes from Hummel et al,[38] who demonstrated that the extent of myocardial viability correlates with the functional response to biventricular pacing in patients with ischemic cardiomyopathy. However, randomized trials are needed to address the relative benefit of revascularization versus medical therapy in patients with hibernating myocardium.

Conclusion

Current practice in decision making regarding reperfusion interventions relies largely or exclusively on the angiographic data. There is evidence, however, that taking into account viability data provided by such modalities as stress and contrast echocardiography, cardiac magnetic resonance imaging[39] and positron emission tomography,[40] may lead to clinical decisions that are better tailored to the risk/benefit profile of each individual patient.

MCE, in particular, is an easily applicable, efficient and diagnostically accurate technique that may provide the clinician with valuable information about the microvascular integrity of a dysfunctional area of the myocardium and the potential for it to recover its function following reperfusion. In the acute event setting, MCE may offer significant prognostic information, contributing to patient risk stratification as well as to the assessment of the success of primary interventions.

However, there is a clear need for large-scale studies to validate the existing data regarding the utility of MCE and provide unequivocal evidence, which will be useful not only for better defining the role of contrast echocardiography in the current management of coronary patients, but also for founding a solid platform of data to support the settling of more "secular" issues, such as the approval of contrast agents for myocardial perfusion imaging, and reimbursement policies, which continue to be a problem in many countries.

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