Myocardial contrast echocardiography in coronary artery disease

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Abstract Myocardial contrast echocardiography (MCE) allows the assessment of myocardial perfusion by imaging the coronary microcirculation. The development of new contrast agents and new diagnostic tools for assessing myocardial perfusion by means of MCE has led to a new field of applications for patients suffering from ischemic heart disease.

Several studies have shown that MCE is a feasible and accurate method to evaluate patients with: a) acute coronary syndromes: MCE is useful before the epicardial reperfusion to delineate the area at risk and to assess the collateral-derived myocardial blood flow, and after the epicardial reperfusion to detect the non-reflow phenomenon; b) chronic coronary syndromes: MCE allows the detection of significant coronary stenosis by means of stress methods and methods without any stress; c) myocardial viability and hibernating myocardium: MCE helps to predict functional recovery of akinetic segments. In these settings, MCE is not only useful as a diagnostic tool but also provides prognostic information.

MCE is a technique in constant development. Among the latest advances we note the development of transesophageal probes with second-harmonic image that allows assessment of myocardial perfusion in a more accurate way. This technique should introduce MCE into new clinical fields, especially the evaluation of myocardial perfusion during cardiac operations. Another recent development is in parametric imaging techniques. These consist in obtaining time curves for all the pixels in the image instead of working only with a few separate regions of interest. A parameter scan is computed for any pixel showing their value as a color overlay in the parametric image.

Summarizing, we can say that MCE is crossing from the experimental laboratory to the daily clinical practice for the evaluation of ischemic heart disease. MCE provides an interesting tool that offers the potential of a complete evaluation of patients with chronic coronary artery disease. This includes both diagnostic and prognostic evaluation.

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Introduction

The development of new contrast agents and new tools for assessing myocardial perfusion by means of Myocardial contrast echocardiography (MCE) has led to a new field of applications for patients suffering from ischemic heart disease. MCE is now crossing from the experimental laboratory to the daily clinical practice for the evaluation of ischemic heart disease, mainly due to the fact that echocardiography has been established as a very important tool for imaging the heart and the great vessels, is available to the cardiologist, and is neither expensive nor time consuming.

MCE allows the assessment of myocardial perfusion (MP) by imaging the coronary microcirculation. Several echocardiographic modalities are available, the main difference between them being the acoustic power needed to perform the study. MP is evaluated by assessing the changes in myocardial videointensity that occur after intravenous contrast injection. Evaluation of these patients is performed by different techniques.

This article will discuss applications of MCE in coronary artery disease.

Acute coronary syndromes

To date, the best studied coronary syndrome is acute myocardial infarction. In recent years, reperfusion therapy has been the cornerstone of the initial treatment of acute myocardial infarction. Nevertheless, it has been demonstrated that restoration of normal flow in the epicardial coronary arteries does not always lead to improvement of myocardial perfusion because, sometimes, microvascular damage and obstruction persist and hamper the reflow to the myocardium. MCE can be very useful for assessing microvascular function: it can define the area at risk during acute coronary occlusion and can evaluate the presence of microvascular damage after reperfusion therapy.

It has been demonstrated in experimental models that approximately 30-45 min after coronary occlusion, myocardial necrosis is initiated in the subendocardium and progresses to the epicardium over time. If patency of the infarct-related artery is restored shortly after occlusion, a subendocardial infarction can be demonstrated, but transmural necrosis will develop if coronary occlusion persists. MCE is the first technique to allow definition of the risk area in real time. This risk area can be defined not only by means of intracoronary administration of the contrast agent but also by means of peripheral intravenous administration of contrast agents.

Utility of MCE before epicardial reperfusion

The value of MCE for delineation of the area at risk is well established (Fig. 1). A multicenter European trial showed a high sensitivity of intravenous MCE for the detection of perfusion defects in patients with total occlusion of the infarct-related vessel, especially for anterior AMI. Patients in this study underwent serial perfusion studies before and after primary angioplasty. In patients with anterior acute myocardial infarction, evaluation of perfusion defects was feasible on admission in 100%; in the remaining patients, who had an inferior acute myocardial infarction, diagnosis was feasible in 84%. All patients with anterior acute myocardial infarction showed a perfusion defect, except three patients who had the infarct-related artery opened in angiography with a TIMI flow grade III. The results of MCE in inferior AMI were not as accurate for this purpose as 13 of 23 patients did not show a perfusion defect in spite of a TIMI flow grade 0 in angiography. Although these results could be explained partly by the presence of collateral circulation, they may also be related to the existence of a smaller area at risk in inferior acute myocardial infarction that would be more difficult to diagnose with MCE.

In daily practice, MCE allows us to triage patients with acute myocardial infarction on the basis of the risk area, because it depends not only on the infarct-related artery but also on the presence or absence of collateral flow, and MCE is very useful...
for identifying collateral perfusion in the presence of an occluded infarct-related artery.

Assessment of collateral-derived myocardial blood flow (MBF) is useful for determining the prognosis of patients with myocardial infarction in the acute phase and for choosing the type of revascularization therapy. Myocardial tissue with residual blood flow can be spared from necrosis even during persistent coronary occlusion lasting several days, although this low level of MBF may not be enough to maintain normal regional systolic function. In such patients, revascularization of the infarct-related artery may lead to an improvement of regional function, as shown by Sabia et al.; in this study, MCE was performed to assess the percentage of the infarct bed perfused by collateral flow in 43 patients who had had an acute myocardial infarction 2 days to 5 weeks earlier and were referred to the catheterization laboratory for coronary angiography. Of the patients who had successful angioplasty, those with more than 50% of the infarct bed supplied by collateral flow had better wall motion and greater improvement in wall motion at follow up than those with less than 50% of the bed supplied by collateral flow. The degree of improvement in function was not influenced by the length of time between the infarction and the attempted angioplasty.

MCE has also provided a basis for the "open-artery hypothesis": it suggests that a patent infarct-related artery confers a survival benefit greater than that expected from myocardial salvage alone. For this reason, MCE can play a role in the prognostic evaluation of patients with non-reperfused acute myocardial infarction, determining potentially viable segments and selecting patients who could benefit most from a delayed angioplasty of the infarct-related artery.

Utility of MCE after epicardial reperfusion

MCE has demonstrated its usefulness for the evaluation of the no-reflow phenomenon. After thrombolysis or primary angioplasty for the treatment of an acute myocardial infarction, epicardial flow may improve but it is not always followed by a restoration of myocardial flow. MCE, when administered by intracoronary injection or by intravenous injection, helps to detect this phenomenon. Although intravenous MCE may show a lower detection rate in low-perfusion areas, it could be more reliable, because it is performed in more physiological conditions than intracoronary MCE.

Chronic coronary syndromes

Evaluation of coronary stenosis using stress tests

Coronary arteries with stenosis of 50%–85% of the coronary luminal diameter show a decreased hyperemic response when myocardial oxygen demand is increased (Fig. 2). Different stress modalities may be used for MCE. Exercise stress is probably the most frequent stress protocol for assessing inducible abnormalities in left ventricular wall motion, but it has rarely been used for MCE due to its inherent technical limitations. Vasodilator stress results in a lower peak heart rate as compared with exercise or dobutamine, and facilitates acquisition of triggered myocardial contrast echocardiography images.

Fig. 2. Myocardial perfusion study (a) in rest conditions and (b) after dipyridamole infusion. The rest study shows normal myocardial perfusion. After dipyridamole infusion an apical perfusion defect appeared at the apical level. Abnormalities in the segmental contraction at this level were also detected.
By administering adenosine, myocardial blood flow is progressively increased. In this setting, myocardial blood flow velocity reserve is proportional to microbubble velocity reserve as assessed by intracoronary Doppler flow wire. Thus, myocardial blood flow reserve may be determined using myocardial contrast echocardiography. Patients with a coronary stenosis greater than 70% have a myocardial blood flow reserve of less than 1.5.

The presence of myocardial perfusion defects is the hallmark of coronary artery disease, and its presence and magnitude have been strongly related with life expectancy and symptomatic prognosis. Evaluation of myocardial blood volume is performed by examining the changes in signal videointensity of the myocardium that occur after intravenous injections of contrast. Because reduction in myocardial blood flow is associated with a reduction in myocardial blood volume, estimation of myocardial blood volume can provide information regarding the severity of coronary stenosis. In the vascular bed supplied by a stenosed coronary artery, myocardial blood volume is decreased when hyperemia appears.

It is possible to visualize and quantify the amount of myocardium that is at risk due to moderate or severe coronary stenosis. Many studies compared MCE with radionuclide imaging. Kaul et al. demonstrated that the location of reversible and irreversible perfusion defects with MCE is similar to that provided by single-photon emission tomography. Their sensitivity and specificity in detecting segments with abnormal perfusion is 92% and 84%, respectively. Two recent papers have reported results that confirm these findings.

Assessment of transmural differences is another method to quantify the severity of stenosis using myocardial contrast echocardiography. One important advantage of MCE over other diagnostic tools for the detection of coronary artery disease is its excellent spatial resolution. Myocardial perfusion is more often impaired in the subendocardial than in the subepicardial layers. This feature provides us with a very accurate method to evaluate the distribution of myocardial blood flow which can be used to quantify the severity of stenosis during stress tests. Then subendocardial endocardium has the highest susceptibility to ischemia. In the presence of coronary artery disease, increases in epicardial blood flow exceed that of the endocardium, resulting in decreases in the endocardial-epicardial ratio of blood flow.

It has been reported that a combination of wall-motion analysis with myocardial contrast echocardiography has the best balance between sensitivity (86%) and specificity (88%), with the highest accuracy (86%). Combined assessment of myocardial perfusion and left ventricular systolic function can improve the accuracy in the detection of ischemic myocardial areas. So, MCE is an important addition to classic stress echocardiography.

**Evaluation of coronary stenosis without stress**

Epicardial blood flow is variable during the cardiac cycle. Flow is higher during diastole than during systole. Retrograde displacement of blood should increase in systole when intramyocardial arterioles are compressed, and the ratio systolic/diastolic myocardial blood volume increases with the presence of an epicardial coronary stenosis. It could be measured by MCE and could be used to detect coronary stenosis at rest, without the need of any stress.

**Myocardial viability**

Identification of viable myocardium allows better selection of patients who need revascularization. It has been reported that myocardial viability can be assessed based on the presence of myocardial contrast enhancement as that depends on microvascular integrity: necrosis of myocardial cells results in collapse of the surrounding microvasculature. Recent studies in post acute myocardial infarct patients have shown a good agreement between MCE and nuclear imaging for the detection of myocardial perfusion.

In the setting of acute myocardial infarction, the detection of microvascular integrity can be very useful in identifying the presence of viability. In a series of patients with acute myocardial infarction, those with evidence of absent intramyocardial flow showed worse ventricular function than those with successful reperfusion. In patients with recent myocardial infarction, Sabia et al. demonstrated that recovery of systolic function after reopening of the epicardial vessel was significantly better in patients with intramyocardial collaterals within the risk area, as assessed by intracoronary contrast injection in non-infarct-related artery.

**Hibernating myocardium**

In the setting of chronic left ventricular dysfunction due to chronic coronary artery disease, MCE helps to differentiate hibernating myocardium from myocardium with irreversible dysfunction. It has been reported that in patients with recent myocardial infarction, MCE allows to identify the presence of viable myocardium after a myocardial infarction. Sensitivity and specificity in identifying post-infarct viable segments with...
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Functional recovery at follow-up were, respectively, 100% and 46% for myocardial contrast echocardiography, and 71% and 88% for dobutamine stress echocardiography. Thus, it is shown that if microvascular integrity is preserved within the post-infarct risk area then contractile reserve and functional recovery can be present at follow-up. In the presence of anatomical damage to the microcirculation, contractile reserve and functional recovery are not present. In another study, performed in patients after acute myocardial infarction, MCE improved sensitivity of dobutamine stress echocardiography for the detection of myocardial viability from 59% to 79%, and negative predictive value from 88% to 95% when MCE showed homogenous contrast opacification in dobutamine non-responsive segments.

New frontiers

Among the latest advances in the field of MCE, we note the development of transesophageal probes with second harmonic image. This allows more accurate assessment of myocardial perfusion, as the images are acquired from a closer window. This technique should introduce MCE into new clinical fields, especially the evaluation of myocardial perfusion during coronary artery bypass graft operations (Fig. 3).

Another recent development is the possibility of displaying MCE data in an attractive way: the so-called parametric imaging. It consists in obtaining time curves for all the pixels in the image instead of working only with a few separate regions of interest. A parameter scan is computed for any pixel showing their value as a color overlay in the parametric image (Fig. 4).

Conclusion

MCE is now crossing from the experimental laboratory to daily clinical practice for the evaluation of ischemic heart disease. It provides an interesting tool that offers the potential for a complete evaluation of patients with chronic coronary artery disease. This includes both diagnostic and prognostic evaluation.

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