Contrast Echocardiography: A New Method for the Assessment of Myocardial Perfusion in Coronary Artery Disease

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Echocardiography is a method highly suited to the non-invasive assessment of myocardial function. Changes in myocardial perfusion can be depicted by echocardiography indirectly as wall motion and thickening abnormalities. Regional left ventricular systolic function estimation is useful in the detection of ischemic but viable myocardium and provides information of paramount importance concerning the management of patients with ischemic cardiomyopathy. During the past several years through advances in contrast agents and ultrasound technology, myocardial contrast echocardiography (MCE) has reached the stage where it is able to detect and evaluate coronary artery disease based on an evaluation of the myocardial perfusion.

Left ventricular dysfunction due to coronary artery disease does not necessarily suggest myocardial necrosis[1]. Dysfunctional but viable myocardium may be the consequence of aprolonged ischemic episode or chronic hypoperfusion unrelated to the coexistence of myocardial necrosis and b. to chronic coronary artery disease with or without reduction of the systolic function[2]. The methods used in the clinical setting for detection of ischemia and the evaluation of myocardial viability that will correspond to invasive techniques, are positron emission tomography (PET)[3], ^{201}Tl[4] or technetium-99m[5], single photon emission computed tomography (SPECT) and low dose dobutamine stress echocardiography (DSE)[6]. Recent data proved that other techniques such as contrast-enhanced magnetic resonance[7] and MCE[8,9] can be used to assess dysfunctional myocardial tissue and hence to predict which patients will benefit from revascularization techiques. This review focuses on the value of MCE in assessing myocardial perfusion in patients with coronary artery disease.

Basic principles of contrast echocardiography for the assessment of myocardial perfusion

The study of myocardial perfusion with echocardiography involves the intracoronary or intravascular injection of contrast agents that can scatter ultrasound[9]. Ultrasound contrast agents consist of microbubbles with a diameter of <5 μm, which contain air or high molecular weight gas. These microbubbles can pass easily through the pulmonary circuit and concentrate in different regions of the myocardium reflecting the relative myocardial blood volume within the myocardial microvasculature. Special interaction techniques between ultrasounds and microbubbles of contrast agents permit the

amplification of the ratio echo signal/noise[10]. Thus, it is possible to estimate the tissue supply on the level of oxygen transfer to the myocardiac cells, and the functional situation of myocardial microcirculation[11].

The echo signal amplification techniques used in MCE are contrast harmonic imaging[12], power Doppler harmonic imaging[13], pulse inversion Doppler harmonic imaging[14] and the combination of power and pulse inversion Doppler harmonic imaging[15]. Ultrasonic excitation of bubbles causes their destruction. The emission of echo signal can be continuous or discrete. Discrete emission per 1st, 2nd, 3rd, etc. cardiac cycles - combined with a high mechanic index - decreases the destruction of bubbles and strengthens the intensity of the echo signal (triggering imaging)[16]. End-systole is preferred for the evaluation of perfusion as the myocardial wall is thicker and a better qualitative and quantitative analysis of depiction of the region of interest is obtained. Continuous emission - combined with a low mechanic index - causes a more restricted destruction of bubbles and provides the possibility of depiction of perfusion in real time. The advantage of continuous emission is that both parameters, myocardial perfusion and wall motion, can be evaluated simultaneously[17].

Role of contrast echocardiography in coronary artery disease

Detection of coronary artery disease

When the epicardial stenosis exceeds 85% myocardial autoregulatory process represent the primary mechanism by which coronary flow remains constant at rest[18]. Hence, arterioles dilate so as to balance the decrease in arteriolar resistance with the increase in trans-stenotic resistance, allowing blood flow to be maintained at normal resting levels[19]. During hyperemia however, the compartment with the highest resistance to myocardial blood flow has shifted from the arterioles to the capillaries. As a result, the increase in capillary resistance can reduce myocardial blood flow, even in the absence of stenosis. If stenosis is detected, the more severe the stenosis the greater the increase in capillary resistance during hyperemia and the greater the limitation at hyperemic flow[20].

A wide array of imaging techniques are now available with MCE to detect coronary stenosis by changes evaluated in (a) myocardial blood volume, (b) myocardial blood flow, or both.

Approximately 90% of myocardial blood volume is contained in the capillary vessels. When the infusion of a contrast agent is continuous, microbubbles remain almost entirely intravascular. Consequently, myocardial videointensity in different myocardial beds reflects the myocardial blood volume in these beds. During hyperemia, capillary blood volume decreases distally to a stenosis resulting in a reduction of the myocardial videointensity in the bed supplied[21] by the stenosis and which is manifested as a perfusion defect upon MCE.

Experimental[21,22] and clinical studies[16,23-26] have proved the ability of MCE to evaluate the presence and the extent of coronary artery disease during the infusion of vasodilators or inotropic agents. Kaul et al[16] compared the ability of MCE to that of 99mTc-scintigraphy, in detecting of ischemia during dipyridamole infusion. The location of the perfusion defects and their determination as permanent or reversible were same with both methods. Excellent concordance was also found between the two methods, when an analysis per segment (92%, k=0.99), per vessel (90%, k=0.77) and per patient (86%, k=0.71) was attempted. The number of patients (30) in this study was limited, while SPECT and not coronary angiography was considered the gold standard. In this study, as in the others mentioned in this review article, the authors reported the limitations of the method, which are analyzed below, in a separate paragraph. Dawson et al[23] using MCE during dipyridamole stress, reported an 85% sensitivity oand specificity of 100%, considering scintigraphic method as the gold standard. Senior et al[24] in a multicenter study of 55 patients with suspected coronary artery disease, found that the diagnostic accuracy of MCE during dipyridamole infusion was 76% in detecting coronary artery stenoses >50%. Shimoni et al[25] published that real time MCE can evaluate myocardial perfusion during exercise echocardiography. Concordance between MCE and both SPECT and exercise echocardiography was 76% and 88% respectively. The analysis of MCE findings was semiquantitative, whereas only a small number of patients underwent coronary angiography. Also, Porter et al[26] published that real time pulse inversion Doppler imaging can detect myocardial perfusion abnormalities during dobutamine stress echocardiography in all patients with stenosis >50% in at least one coronary artery. There was an 83% concordance between angiography and MCE and a 72% concordance between MCE and dobutamine echocardiography.

Myocardial blood flow is quantified with the use of triggering imaging as developed by Wei et al[27], in an animal model. It is based on the concept that during a continuous intravenous infusion of a contrast agent the destruction of microbubbles by ultrasound and subsequent assessment of the rate of replenishment of microbubbles into the myocardial microcirculation depends on the flow rate and the time between two ultrasound pulses (the pulsing interval). Therefore, when the pulsing interval is relatively short, the degree of microbubble replenishment into a bed subtended by a stenosis will demonstrate a relative perfusion defect compared with a normal bed during hyperemia. The authors showed that myocardial contrast intensity fits an exponential function: $y = A (1–e^{-\beta t})$, where y is the videointensity at pulsing interval of echo signal t, A is the plateau videointensity that represents the myocardial blood volume and b represents the mean of microbubble velocity. The rate of increase in videointensity was slowest at low flow rates and increased with higher flow rates. Later experimental studies [28-30] demonstrated the ability of low-energy real-time perfusion techniques to obtain similar measurements.

Recent studies evaluated the ability of MCE to quantitate myocardial blood flow in humans. Wei et al[31] performed MCE and intracoronary Doppler in healthy volunteers and patients with coronary artery disease. Both methods indicated that the volunteers with normal coronary arteries had significantly higher myocardial flow reserve compared to the patients suffering from coronary artery disease.

They also found significant relation between velocity reserve determined by MCE and the coronary stenosis percentage measured using quantitative coronary angiography ($r=0.79$, $p<0.001$). Ay et al[32] found a significant correlation between MCE - and PET- derived myocardial flow reserve in healthy volunteers during dipyridamole infusion ($r=0.66$, $p<0.01$). Taken together these data indicate that the quantification of myocardial blood flow using MCE is feasible in humans and allows a reliable assessment of the coronary flow reserve. The quantification of myocardial blood flow improved the diagnostic accuracy of MCE (86%) in detecting coronary artery disease compared with the visual analysis of MCE (76%) and the 99mTc-scintigraphy (78%)[33]. Furthermore, MCE can quantitate endocardial or epicardial perfusion separately, according to the experimental study of Linka et al[34].

The detection of coronary artery disease at rest using MCE without an exercise test is also interesting. According to Wei et al,[35] changes in videointensity during systole and diastole can detect and quantify coronary stenoses severity at rest without recourse to any pharmacologic or other forms of stress. A significant increase in systolic videointensity was noted with coronary stenosis that resulted in progressive increases in the systolic/ diastolic videointentsity ratio with greater degrees of stenosis ($p=0,003$). Although the authors found a significant relation between the above parameters, other factors also affect this ratio including a. incomplete myocardial filling during diastole secondary to tachycardia and b. cardiac contraction; catecholamines can increase the ratio, whereas regional dysfunction can decrease it. Aggeli et al[36] also reported a quantitative assessment of myocardial perfusion in human beings at rest, using intravenous injection of Optison and triggering imaging technique.

They conclude that the development of perfusion defects on MCE is related to a decrease in myocardial blood volume distal to a stenosis during hyperemia. Potential use of this approach in a clinical setting includes the noninvasive detection and quantification of coronary stenosis severity, as well as the evaluation of clinical condition associated with impaired coronary flow severe, such as hypertrophy and syndrome X.

Assessment of myocardial perfusion in acute myocardial infarction

The early reestablishment of epicardial coronary patency after thrombolysis or angioplasty is a determined factor for the restriction of the infarct size. Recent data show that coronary reopening does not spontaneously reflect a constant myocardial blood flow, because the necrotic region has variously perfused zones depending on the degree of capillary damage[37]. The microvascular integrity in the infarct area is a necessary requirement of salvage myocardium and it depends on the duration of ischemic period and the residual flow in the region.

Capability of MCE to recognise the presence of viable myocardium is based on the assumption that microvascular integrity is a necessary prerequisite of viability in myocardial infarction. Perfusion abnormalities in the infarct area result in changes in the distribution of microbubbles in the ischemic tissue and the visualization of perfusion defect[38,39]. Ne-

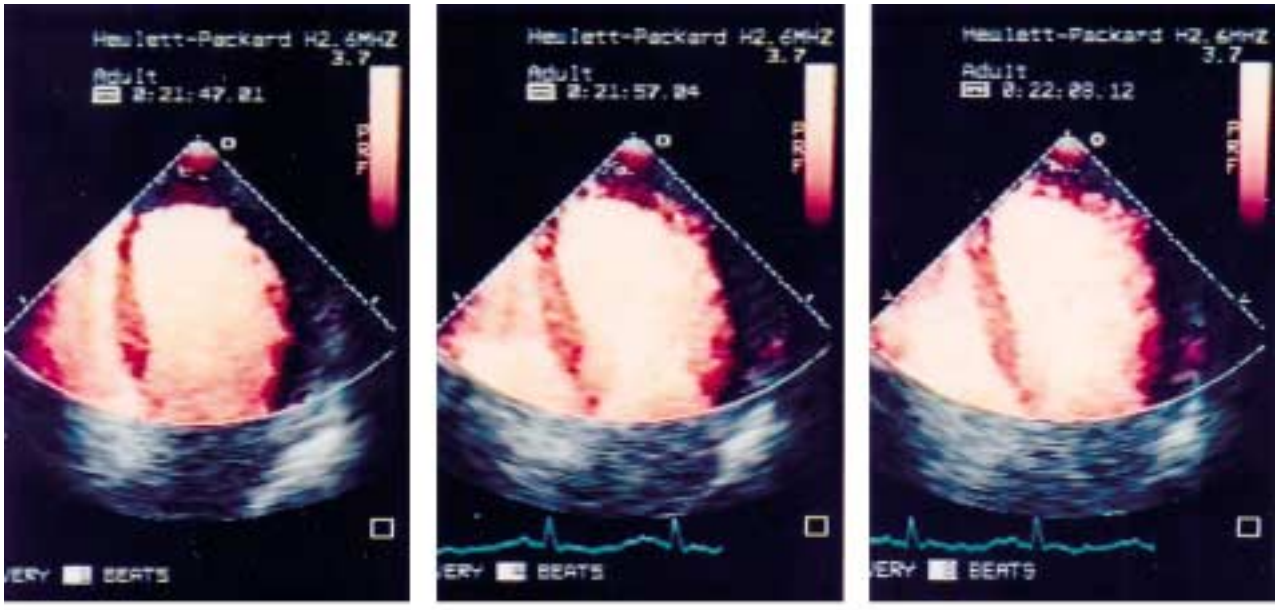

Figure 1. Apical 4-chamber view from patient with acute myocardial infarction with absent contrast opacification in the apex at short triggering intervals, but homogenous opacification with delayed triggering.

vertheless, if collateral circulation has been developed, contrast enhancement varies depending on the extent of collateral circulation[39]. The early visualization of a perfusion defect after an acute myocardial infarction is due to perfusion disturbance on two levels:

a) On the level of the epicardiac artery, where occlusion is due to the rupture of atheromatous plaque and of clot formation inside the lumen. Early studies using intracoronary MCE and subsequent studies with intravenous injection of the contrast agent have demonstrated that this method is useful in assessing reperfusion, manifested as contrast enhancement in the area at risk[37,39,40]. The presence of adequate contrast enhancement is a marker of viable myocardium (Figure 1). Patients with adequate contrast opacification in the infarct area presented improvement of ventricular function and better clinical outcome compared with patients with permanent defects[40,41]. Conversely, if the coronary artery occlusion is still in existence, the size of the perfusion depicts the area at risk, according to Coggins et al[42]. The repetition of MCE shortly after reperfusion and the comparative study of defects provide a simultaneous estimation of both, myocardial microcirculation and the success of therapeutic intervention[43]. Increased contrast enhancement in the infarct area after reperfusion, during a time period that reactive hyperemia has receded, reflects preserved microvascular integrity, according to Rovai et al[44]. In another study, the delayed opacification in the infarct area with triggering imaging, regardless of the severity of residual stenosis of the infarct related artery, was an important marker of regional recovery[45]. In this study, semiquantitative analysis limited the interpretation of MCE in inferoposterior segments, thus leading to higher false negative results in these segments. Also, a prolongation (>1:10) of triggering intervals would possibly increase the sensitivity in detecting viable myocardium.

b) On the level of microcirculation, where despite the achievement of adequate coronary recanalization at angiography, trivial or absent enhancement in the myocardial downstream may be observed. In these cases, the normal flow on the level of microcirculation is not feasible because of the decreased number of capillaries (low or no-reflow phenomenon). Observations with the electronic microscope of the reperfused infarct area showed endothelium damage, cellular and interstitial edema, neutrophil accumulation and microvascular embolization[46].

In a study by Ito et al[40], partial opacification within the infarct area was seen in most patients with TIMI flow grade 2 after successful reopening of the in-

farct-related artery and in 1/3 of patients with TIMI flow grade 3 because of the low or no-reflow phenomenon. Among patients with TIMI 3 flow, significant improvement in ventricular function and better prognosis during follow-up was observed only in patients with adequate contrast opacification within the risk area. These findings are consistent with the results of Stone et al[47] in a later study. The authors concluded that the adequate opacification in the infarct area was predictor of its functional recovery, regardless of the information provided by the angiographic data. According to Lepper et al[41], patients in whom no-reflow phenomenon was not evident, presented myocardial perfusion by MCE, had better coronary flow reserve 24 hours after angioplasty, as well as improvement of ventricular function 1 month later compared to those with no-reflow. It is therefore concluded that MCE is a reliable method for the assessment of coronary flow reserve and the prediction of late ventricular functional recovery after myocardial infarction. One of the main limitations of this study, beyond the small number of patients (25), was that in experimental studies an initial reduction of coronary flow reserve after reperfusion was followed by a period of subsequent recovery lasting up to 1 week.

In another study, Ito et al[48] investigated the clinical implications of no-reflow phenomenon using intracoronary MCE after reperfusion, in 126 patients with anterior wall acute myocardial infarction. They found that 47 patients (37%) did not present opacification within the infarct area. These patients, had a higher likelihood of presenting congestive heart failure and pericardial effusions early after myoacardial infarction. The authors concluded that the patients with circumscribed perfusion defects pertinent to no reflow phenomenon present larger infarctions, progressive dilatation of the left ventricle and more often, complications. In this study, only in-hospital complications were recorded, while the quality of life and the long-term prognosis in these patients were not taken into consideration.

Sakuma et al[49] performed primary angioplasty in 72 patients after acute infarction, trying to determine the suitable time for performing MCE in order to predict the ventricular recovery early. The patients were examined successively before, immediately after, as well as on the 2nd and the 21st days following reperfusion. The authors concluded that the examination on the 2nd day after reperfusion provided reliable information on the state of the coronary microcirculation and the prediction of late functional recovery.

In the acute myocardial infarction, the sensitivity of MCE in predicting recovery of function after reperfusion varies from 62% to 96%, with low to medium sensitivity (18-67%) and high negative predictive value[45,50,51]. Studies compared MCE with dobutamine stress echocardiography have shown higher predictive accuracy - particularly specificity - for recovery of function using contractile reserve. Galiuto and Iliceto[9] studied 24 patients with recent myocardial infarction with MCE and a low dose dobutamine stress echocardiography for detecting viable myocardium. The sensitivity and specificity were 100% and 46% for MCE and 71% and 88% for dobutamine stress test. The higher accuracy of dobutamine stress test can be attributed to the fact that a). MCE overestimates the residual viability because arterioles and venules may be preserved even in the presence of an infarction and b). MCE detects residual viability that is underestimated by resting regional function.

Detection of hibernating myocardium in coronary artery disease

Often in patients with chronic coronary artery, disease impairment of contractile function has been regarded as a protective mechanism by which the heart spontaneously downregulates its function, minimizes its energy requirements and prevents the appearance of irreversible tissue damage. Myocardial hibernation describes such a state whereby restoration of coronary flow allows recovery of ventricular contractile functions[52]. Patients with hibernating myocardium appear to be at increased risk for future cardiac events[53]. Therefore, the detection of viable myocardium in patients with ischemic cardiomyopathy is important.

Unlike acute coronary syndromes, only a few studies have evaluated the role of MCE in myocardial hybernation. De Filippi et al[54] and Nagueh et al[55] showed the effectiveness of intracoronary MCE in detecting hibernating myocardium. Nagueh et al[55] report high sensitivity (89%), but low specificity (43%) of the method to predict recovery of myocardial function after reperfusion in patients with left ventricular ischemic dysfunction. The predictive accuracy was similar to that of thallium scintigraphy. Aggeli et al[56] found that harmonic power Doppler imaging with intravenous injection of Levovist had

similar accuracy (74%) with dobutamine stress test (79%) in predicting functional recovery after coronary bypass surgery. In a recent study, Shimoni et al[57] found that using the parameter of quantification of blood flow with MCE as an indicator of viability, the total sensitivity (90%) and specificity (61%) were improved compared to those of dobutamine stress test (80% and 54%, respectively). However, the main disadvantage of the above mentioned studies is the small sample of population that was examined. Large-scale clinical studies are needed to evaluate the supplementary importanceof MCE to current echocardiographic methods in evaluating myocardial viability in chronic ischemic heart disease.

Limitations of contrast echocardiography in the evaluation of myocardial perfusion

A number of technical or physical limitations of the MCE affect both the accuracy and the feasiblility of this method[58]. Low image quality in the basal segments and overestimation of perfusion in the apical segments are the main limitations of MCE at present. On the other hand, MCE can evaluate myocardial perfusion abnormalities in a percentage 80%-95% and these findings are similar to those assessed by positron emission tomography (PET) according to Muro et al[59]. It is expected that in the future the quantitative analysis will permit a more precise evaluation of myocardial perfusion in comparison with the qualitative analysis that is widely used in clinical practice today. The conditions under which the patient is examined also play a significant role. The patient ought remain in the same position and breathe evenly, so that the images will be comparable at any moment. The triggering method of imaging is not applicable in case of tachycardia (>100 bpm) while other techniques can be also applied during exertion or pharmacologic stress. Doctors with specialized training are also necessary for MCE, while more time is needed both for the examination of the patient and for for the qualitative or, even more the quantitative evaluation of myocardial perfusion.

In conclusion, it can be said that this method has many advantages. The non-invasive evaluation of capillary integrity and of microcirculation function are essential for the clinical doctor and for the management of acute ischemic syndromes and the handling of patients with chronic coronary artery disease. The advantage of MCE in the evaluation of viable myocardium is the high negative predictive value for recovery of left ventricular function. However, further prospective studies are required to evaluate the clinical role of MCE to establish it as a method of reference for the assessment of myocardial perfusion.

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