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Evolving diagnostic and therapeutic applications of ultrasound contrast agents

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Ultrasound contrast agents have been primarily used for improving left ventricular opacification, but there are emerging applications that could significantly increase their utilization. In addition to enhancement of endocardial border detection and Doppler assessment of LV function, contrast echocardiography may be utilized to assess myocardial perfusion and viability. Until now, detection of myocardial perfusion has been almost exclusively done with radionuclide tracers. However, since the myocardial contrast echocardiography (MCE) is safe, less expensive and it can be performed at the patient's bedside there is growing interest in this application. In addition MCE has increased resolution when compared with radionuclide imaging (2 mm vs. 8–12 mm) which permits detection of subendocardial perfusion defects with improved precision. New data indicate that MCE may be used in the emergency department to assist in ruling out acute coronary syndromes [1] and that myocardial perfusion imaging with ultrasound contrast agents during dobutamine stress echocardiography is significantly better than wall motion analysis alone in predicting patient's outcome [2].

MCE has also been used to detect the no-reflow phenomenon. The defect detected before primary PCI can define the region at risk, and the defect detected after successful coronary reperfusion constitute the area of no-reflow. The improvement of myocardial perfusion on MCE was predictive of subsequent improvement in left ventricular function [3]. Assessment of myocardial perfusion and the coronary microcirculation with MCE corresponded to evaluation using coronary flow reserve measurements obtained with a coronary artery Doppler wire. MCE may also provide prognostic information. In one study of 50 patients with a first myocardial infarction who received thrombolytic therapy, the presence of reduced opacification on MCE, performed on day two, predicted a higher major cardiac event rate (death, nonfatal infarction, or admission for congestive heart failure) during a mean follow up of 22 months (28% vs. 4% in those with adequate opacification) [4]. In another study, patients with a persistent defect in the infarct zone due to the no-reflow phenomenon, despite the restoration of TIMI grade 3 flow, had a deterioration of regional and global systolic dysfunction [5]. Current study published by Wita et al. in this issue of Folia Cardiologica contributes significant data. It demonstrates that MCE has high prognostic value for prediction of functional left ventricular improvement in patients with first myocardial infarction and restored patency of target artery. In fact, MCE turned out to be significantly better than currently utilized methods, raising the possibility of MCE becoming the new "gold standard" for evaluation of no-reflow phenomenon.

The role of myocardial contrast echocardiography in evaluation of infarcted, stunned and hibernating myocardium

Dysfunctional segments of the LV following an ischemic insult may represent either necrotic, infarcted tissue, temporary effect of hypoperfusion called stunning or chronically hypoperfused, but still

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viable tissue called hibernating myocardium. Prolonged occlusion of coronary artery leads to myocardial necrosis which may be easily detected as wall motion abnormality on echocardiography. However, if the coronary flow is restored before the onset of myocardial necrosis, the persistent wall motion abnormalities may represent viable but not contractile thus "stunned" myocardium. Since there is a substantial variability in the time course over which myocardium recovers from stunning, ranging from weeks to months, it is good to know that MCE may be helpful in differentiating these two patterns of myocardial dysfunction. Stunned myocardium has homogeneous myocardial contrast, representing normal blood flow with an intact microvasculature. Such a pattern implies either that the decrease in perfusion was not lethal or that reperfusion (either spontaneous or as a result of intervention) occurred prior to necrosis. In this setting, systolic function is likely to return over the next several weeks [6–9]. In one study of 96 patients, the positive and negative predictive value of homogeneous opacification for recovery of contractile function at six months was 47% and 84%, respectively; the positive predictive value for predicting functional recovery was 78% in those who were revascularized [8].

Chronically reduced blood flow may also lead to a state of persistently impaired myocardial function with preservation of viability called hibernating myocardium. Hibernating myocardium can be partially or completely restored to normal by improving blood flow and/or by reducing demand. Viability studies performed to detect hibernating but viable tissue are usually done in high risk patients with LV dysfunction in order to guide difficult decisions regarding revascularization. Current techniques used to determine myocardial viability include single photon emission computed tomography (SPECT) imaging, positron emission tomography scanning, nuclear magnetic imaging, and low-dose dobutamine echocardiography. MCE provides simultaneous LV function and perfusion information and offers the advantages of improved image resolution (over SPECT), portability, cost economy, and practicality. The identification of subnormal flow (heterogeneous contrast effect) as opposed to no flow (fixed contrast defect) or normal flow (homogeneous contrast) within dysfunctional myocardium may predict long-term recovery of function following the restoration of normal blood supply [10].

Microbubbles may also have therapeutic potential. Preclinical trials have demonstrated that ultrasound-mediated microbubble destruction can be used to target delivery of genes to the myocardium [11]. Phase 1 clinical trials are under way exploring whether antisense oligonucleotides, which inhibit c-myc protooncogene can be safely delivered to stented coronary artery segment with intravenous microbubbles. Microbubbles may also be used in combination with ultrasound to non-invasively dissolve intravascular thrombi without the need of a lytic agent [12]. This may be especially useful in the treatment of acute stroke, and preclinical trials have demonstrated that intracranial ultrasound and intravenous target microbubbles can successfully recanalize intracranial thrombi [13].

Myocardial contrast echocardiography is a new and growing field. It started with the quest for improved echocardiographic resolution and left ventricular endocardial border detection and grew into the real time assessment of intracardiac blood flow, myocardial perfusion and viability, and it may provide a future means for drug delivery and other therapeutic interventions.

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