Quantification methods in contrast echocardiography

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Abstract New technologies and the availability of new echo-contrast agents have resulted in advances of diagnostic and prognostic indications of left ventricular opacification (LVO) and myocardial perfusion. The clinical diagnostic value of ultrasound contrast media for LVO and its impact on the clinical decision-making process has been demonstrated in several studies. Recent research aims at developing new quantitative software to improve the delineation of the endocardial border, to assess 3D myocardial perfusion for more accurate regional/global LV function measurements, and to evaluate 4D intra-cardiac flow dynamics. Furthermore, a general consensus has been reached on the incremental value of myocardial contrast echocardiography (MCE) for obtaining additional information in both chronic and acute coronary artery disease (CAD) patients and on the possibility to make quantitative measurements of microvascular damage. Q-contrast\textsuperscript{®} is a new software system which provides quantitative measurements to generate parametric images of microcirculatory flow. In a research project including 120 patients, Q-contrast software has been tested to assess the role of contrast in AMI (Acute Myocardial Infarction Contrast Imaging (A.M.I.C.I. Study); good agreement between parametric MCE and SPECT has been found. Preliminary results further confirm that quantitative MCE may provide additional clinical value over qualitative information for the assessment of LV function and of the effects of coronary artery disease on the myocardial microcirculation (viability, ischemia or infarct).

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Introduction

Myocardial contrast echocardiography (MCE) is a relatively new technique which has expanded the capability of the conventional 2D-Doppler echocardiography in the assessment of left ventricular (LV) function. The recent advances made by both US equipment manufacturers (digitized platforms) and pharmaceutical industry (new echo-contrast agents), have allowed for the development of (A) better endocardial border delineation and (B) assessment of myocardial perfusion.

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Left ventricular opacification

Improved endocardial border delineation may be achieved after left ventricular cavity opacification (LVO) following intravenous injection of contrast. LVO and myocardial perfusion can be obtained during the same session using the same contrast agent and the same equipment\textsuperscript{1,2}.

In recent years several studies have shown the incremental diagnostic value of ultrasound contrast media for LVO and its impact on the clinical decision making\textsuperscript{3,4}. LVO may provide improved information on LV function in those patients in whom imaging is suboptimal and non-diagnostic. Further, LVO may improve quantification of left ventricular function in approximately 50% of patients, by
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Fig. 1. 4-chamber view, the apical thrombus is well visualized only in the contrast-enhanced image (bottom).

providing better imaging in those patients in whom 2 to 6 adjacent myocardial segments (13-38%) are not adequately visualized using standard echocardiography. LVO may also improve inter-observer agreement and reproducibility allowing for a more accurate evaluation of LV volumes when compared to other reference methods, such as MRI.

Application of contrast may also be considered when the following clinical scenarios are suspected: (1) apical cardiomyopathy; (2) the presence of an apical thrombus, tumor or pseudoaneurysm (fig. 1) or (3) left ventricular non compaction.

Research developments for LVO application

Recently new quantitative software applications for LVO have been developed, which can further improve the diagnostic capability of the contrast echo. These are aimed to (1) increase the quality of endocardial border delineation; (2) assess 3D perfusion and regional/global LV function; (3) evaluate 3D intra-cardiac flow dynamics. A very useful tool has been developed in Dr. Tonti's laboratory: starting from low frame rate (20 FR are normally used with contrast) it rebuilds a loop of a single beat at a higher frame rate, almost double that of the original, providing a clear image of endocardial borders. Using dedicated software (Diogenes software) it is possible to combine improved endocardial delineation with additional information on myocardial perfusion with just one set of acquired images (fig. 2).

3D echocardiography is a promising new development but image quality remains inferior to 2D imaging. With 3D image reconstruction, often a number of image frame are eliminated. With the addition of contrast, the endocardial border definition is improved and thus ejection fraction may be better assessed (fig. 2, overleaf). A further new area is assessing LV flow dynamics in 3 dimensions. In Dr Tonti's laboratory, a new software application is currently under development based on mathematical models which, by reducing the contrast infusion rate, allows for the assessment of the intra-ventricular flow dynamics of microbubbles. This has the potential for obtaining detailed information on ventricular contraction, and potential areas of thrombus formation.

Myocardial perfusion

The role of myocardial contrast echocardiography (MCE) in clinical decision-making has recently been emphasized.

A very large study on more than 1000 patients has shown the additional value of MCE in patients presenting in the emergency department with chest pain and no ST-segment elevation. In these patients, the assessment of regional function and myocardial perfusion added a significative prognostic value to routine echocardiography. The study demonstrated that in acute coronary syndrome when abnormal regional function and
perfusion are present in the same patient the survival rate is greatly reduced.

In the setting of detecting CAD, several studies have shown the additional value of MCE over wall motion abnormalities alone during stress echocardiography. In particular, a recent large study showed a close correlation between perfusion, wall motion and survival rate. If both perfusion and wall motion are abnormal the survival rate is dramatically reduced.

All these studies clearly underline the incremental value of MCE in providing complementary information over and above other more established methods, such as nuclear imaging, both in chronic and acute CAD patients.

Clinical applications of parametric imaging (Qcontrast®) using SonoVue - Our experience

Transducer developments and the introduction of new ultrasound contrast agents have made possible the quantitative evaluation of microvascular damage. "Q-contrast" is a new software application developed for parametric imaging in our laboratory. In brief, with an innovative algorithm it is possible to obtain replenishment curves for all points of the scan plane at any one time. The spatial distributions of the perfusion-related parameters \( A, \beta \) and \( A \times \beta \) are shown in an image format. The values from each pixel are color-encoded relative to the mean value. From parametric image reconstruction, the area of contrast defect may be calculated using a four-color map segmentation; the blue area, corresponding to the largest clearly demarcated contrast defect, may be traced manually (fig. 4). Contrast defect area (CDA%) is expressed as a percentage of the total LV area.

Methodology

From native MCE images, the length of endocardial border corresponding to the segment with contrast defect (CDL) may be measured in the 2, 3- and 4-chamber views. The sum of both endocardial border lengths defined the size of the perfusion defect. The following formula is used to assess the relative CDL%:

\[
\frac{\text{Total residual CDL after reperfusion}}{\text{Total length of endocardial border}} \times 100
\]

This software was first tested using different US equipments on 5 pigs given sulphur hexafluoride bubbles (1 ml/min) and fluorescent microspheres (reference) after the induction of
50% and 100% stenosis of left anterior descending coronary artery\textsuperscript{22}. A close correlation was found between the ratio risk area/control area by microspheres and the equivalent ratio risk area/control area ($SI \times \beta$) by MCE, being approximately 0.9 for any contrast modality tested\textsuperscript{22}.

**Study design**

Parametric MCE and SPECT were compared in 12 patients with recent myocardial infarction, including 119 segments\textsuperscript{22}. Agreement amounted to 83\% (kappa: 0.53 for peak SI and 0.55 for $SI \times \beta$). The sensitivity and specificity of peak SI to detect abnormal segmental tracer uptake were 67\% and 88\%; the values for $SI \times \beta$ were 70\% and 87\%.

Q-contrast software has then been tested in a large-scale clinical research project to assess the role of contrast in AMI (Acute Myocardial Infarction Contrast Imaging – A.M.I.C.I. – Study). The study involving 12 centres in Italy enrolled patients with ST-segment elevation acute myocardial infarction (STEMI). The clinical impact of quantitative parameters derived from myocardial contrast echocardiography was evaluated. The aim of the study was:

1. To address the influence of different recanalization strategies on the extent and time-course of microvascular damage, as assessed by quantitative MCE.
2. To compare quantitative MCE parameters with TIMI grade, ECG and clinical markers in identifying failed reperfusion after reperfusion treatment.
3. To assess temporal changes of myocardial perfusion flow in the risk area in the early period following STEMI, and their relation to early and late regional functional recovery.
4. To explore the additional role of perfusion impairment over segmental wall motion extension to predict left ventricular remodelling after AMI.

Patients with first STEMI presenting within 6 hours from symptom onset underwent MCE with SonoVue\textsuperscript{®} before and after different reperfusion strategies (primary or facilitated PCI or thrombolysis), at pre-discharge and at 3 months follow-up. The study protocol is summarized in Table 1.
Quantitative analysis was performed on MCE images after coronary reflow and at pre-discharge using Q-contrast® software (Bracco Imaging), as previously described.  

Results  
From January 2003 until May 2004, 120 patients were enrolled. Mean age of the patient population was 59±10 years. Significant ST-segment reduction was present in 66% of patients. Infarct area was in the LAD territory in the majority of patients (87%). Sixty-two percent of them underwent primary PCI, but only 19% had a completely normal myocardial reflow after reperfusion. Two parameters described the extent of myocardial disease: the contrast defect area and the contrast defect length. The analysis of the echocardiographic characteristics of our patients population showed that mean contrast defect area and contrast defect length are lower than the extent of wall motion abnormalities; suggesting that soon after reperfusion, a portion of infarct area is normally perfused.  

To evaluate the success of coronary reperfusion, microvascular perfusion was assessed vs ST-segment changes and coronary artery reflow. After dividing our population according to % ST-segment reduction (fig. 5), the extent of regional wall motion abnormalities (RWMA) was the same in the 2 subgroups of patients soon after reperfusion, and at follow-up it is reduced only in patients with ST reduction. Conversely, extent of contrast defect was already lower in patients with ST reduction at baseline, gradually decreasing at follow-up; therefore the extent of contrast defect is a better predictor of coronary reperfusion than wall motion abnormality. Similar results were obtained dividing our population according to coronary TIMI grade after reperfusion (fig. 6). There was no difference in RWMA in TIMI 2 vs TIMI 3 patients after reperfusion. On the contrary, the extent of contrast defect after reflow was lower in TIMI 3 vs TIMI 2 group and it reduced in the course of time (fig. 6). The extent of contrast defect best correlated with ejection fraction and regional function at follow-up. Another important parameter to evaluate the success of coronary reperfusion was the amount of left ventricular remodeling. Dividing the population according to presence of LV remodeling the extent of contrast defect best correlated with ejection fraction and regional function at follow-up.
which provides the best results in terms of coronary artery disease. Further potential on the myocardial microcirculation that quantitative MCE may provide additional clinical value over qualitative information in the assessment of left ventricular function and myocardial damage. 8. Bar graph showing the study population divided according to presence of LV remodeling at follow-up. The extent of contrast defect (CDL%) after reperfusion is highly predictive of early and late LV remodeling.

Finally, the evaluation of the extent of contrast defect may have a strong impact on patient management over the extent of RWMA. As shown in fig. 8, the evaluation of the extent of contrast defect allows for the identification of the most effective reperfusion strategy after acute myocardial infarction, i.e., the facilitated PCI which provides the best results in terms of coronary reperfusion.

Conclusion

In conclusion, preliminary results further confirm that quantitative MCE may provide additional clinical value over qualitative information in the assessment of left ventricular function and the effects on the myocardial microcirculation (viability, ischemia or infarct) of the presence of coronary artery disease. Further potential application of quantitative MCE may explore the microcirculatory function in non-coronary physiopathological models (such as arterial hypertension, diabetes).

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