



Clinical application of quantitative analysis in real-time MCE

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KEYWORDS

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Myocardial perfusion;
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Abstract The introduction of stable microbubble contrast agents and technological advances have recently made it feasible to perform quantitative measurements of microvascular damage by myocardial contrast echocardiography (MCE). *Qontrast*[®] is a new software system for such measurements. It includes physiological filters, global rescale, regional rescale, automatic myocardial tracking, manual ECG trigger and parametric imaging.

Qontrast[®] was tested 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. The image sequences were repeated four times using different ultrasound (US) equipment. 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.

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

Parametric MCE is a promising imaging technique for the assessment of myocardial perfusion in patients with suspected or known coronary artery disease.

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Introduction

Several recent studies have underlined the key

role of microcirculatory disorder in ischemic heart disease¹. The extent of microvascular damage as assessed by myocardial contrast echocardiography (MCE) provides valuable diagnostic and prognostic information for the management of patients with coronary artery disease (CAD)¹⁻¹³. This technique allows assessment of the severity of microvas-

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cular damage in patients with acute myocardial infarction (AMI) after recanalization of the infarct-related artery that is an independent predictor of left ventricular remodeling. At the same time, dysfunctioning but still viable myocardial tissue after AMI that will benefit from revascularization in terms of functional recovery and survival may be accurately assessed by MCE. Similar data may also be obtained by coronary angiography using TIMI grade and myocardial blush, but the quality of MCE images is much higher.

The information that MCE provides on myocardial tissue perfusion can also be used to assess myocardial salvage after reperfusion, coronary stenoses, and the presence of collateral circulation in the myocardial tissue area at risk¹⁻¹³.

The introduction of stable microbubble contrast agents and technological advances have enabled the visualization of contrast in the coronary microvasculature even during low-energy real-time imaging, allowing simultaneous assessment of wall motion and myocardial perfusion¹⁴⁻³³. By this method, microbubble replenishment curves may be obtained that provide quantitative measurements of regional microcirculatory blood flow^{34,35}.

In a recent study in which MCE quantitative findings were correlated to histological findings, a close correlation was found between MCE data and microvascular density, capillary area, as well as collagen content³⁶.

Preliminary data showed that quantitative analysis of digital data provides more accurate diagnostic MCE information than does qualitative analysis of video signal intensity³⁷.

The objective of this paper is to present the results obtained with the new software system *Qontrast*[®]³⁸ for quantitative analysis of real-time MCE images.

Qontrast[®] software

The development of software for quantitative analysis of MCE images involved the solution of a number of problems. The main problem was the non-uniformity of myocardial contrast enhancement, which is due to the non-uniformity of bubble destruction in ultrasound fields. Additional issues were lateral field drop-out, partial apical bubble destruction, basal attenuation, and acoustic window dependence (Fig. 1).

To reduce the effects of these factors we introduced³⁸ (Fig. 2):

- *Physiological filters* for avoiding the problem of destruction failure, i.e. failure to destroy all bubbles during the flash.

Myocardial Contrast Echo

Main problems to be solved

- Non-uniform myocardial contrast enhancement
- Non-uniform bubbles destruction
- Lateral field drop-out
- Partial apical bubble destruction
- Basal attenuation
- Acoustic window dependence

Fig. 1. Main problems to be solved for MCE.

Qontrast[®] solutions

- *Physiological filters*: destruction failure
- *Global Rescale*: % maximum myocardial SI in each view
- *Regional Rescale*: % maximum relative cavity SI
- *Automatic myocardial tracking*: no ROI adjustment
- *Manual ECG trigger*: manual frame selection
- *Parametric Imaging*: Peak SI, RT, β , Slope
 - color map segmentation
 - refilling curves

Fig. 2. *Qontrast*[®] solutions.

- *Global Rescale*, which involves normalization of the signal observed as a function of the maximum signal intensity (SI) in each view; in other words, for any scan or view, the signal is rescaled with the maximum intensity reached in that view.
- *Regional Rescale*, which involves rescaling of the signal on the tissue with the maximum SI locally reached in the neighboring cavity sector (from wall to the axis) in that view, because energy is not uniform in the cavity, so the signal is related to the energy of bubble destruction.
- *Automatic myocardial tracking*, which means that no manual adjustment (frame by frame) of the region of interest (ROI) is needed, because the system is able to automatically recognize the border of the myocardium. This feature resolves the issue of wall-motion artifacts³⁹ (Fig. 3).
- *Manual ECG trigger*, allowing manual removal of unwanted frames in which the quality of the bubble signal is reduced by a deep breath, probe motion or attenuation.
- *Parametric imaging* which enables the calculation, and imaging on the entire scan plane, of the peak signal intensity (SI), the refilling time (RT), the frequency of SI rise ($\beta = 1/RT$) and the rate of SI rise, or refilling slope, given by the product $SI \times \beta$.

This technique rapidly yields a perfusion map subdivided into segments with different colors corresponding to different SI, following the SPECT color code (Fig. 4). Parametric imaging is very simple to read, and refilling curves may be obtained in a few seconds point by point. In this way, quantitative MCE-derived

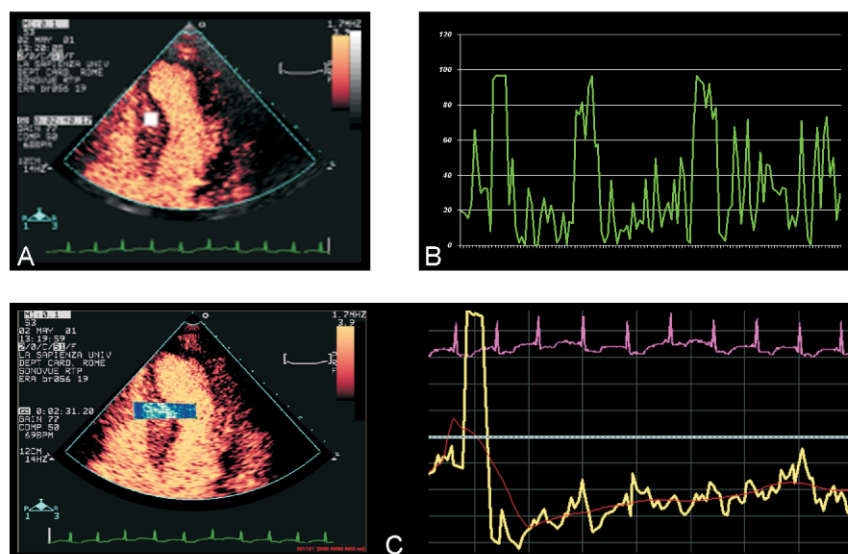


Fig. 3. The problem of wall motion: Qontrast®.

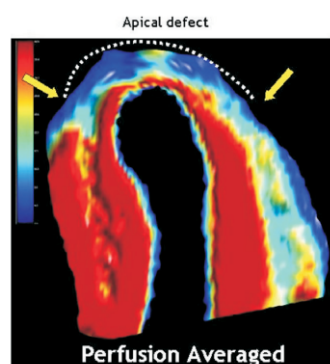


Fig. 4. Qontrast® software-parametric imaging.

parameters, evaluating myocardial blood volume (peak SI), myocardial blood flow velocity (β) and myocardial blood flow ($SI \times \beta$) may be calculated in each segmental region.

However, quantitative analysis is a very complex technique and not all issues have been resolved. Reproducibility is not fully satisfactory, as inter-individual variability has been observed. This issue stems from the intrinsic nature of ultrasound imaging, which is highly dependent on operator skill. Since bubble resonance is strictly dependent on the insonating energy, the scan plane with the best myocardial opacification should be chosen carefully. Operator-related variability is a considerable disadvantage that cannot be removed. Another issue is the lack of sufficient data at present to determine the sensitivity and specificity of the method.

Another problem is the *non-homogeneous contrast opacification*. Although we would like to have a homogeneous medium, this is usually not the case. The 3D reconstruction in Fig. 5 shows that the brightness of the signal is different in different

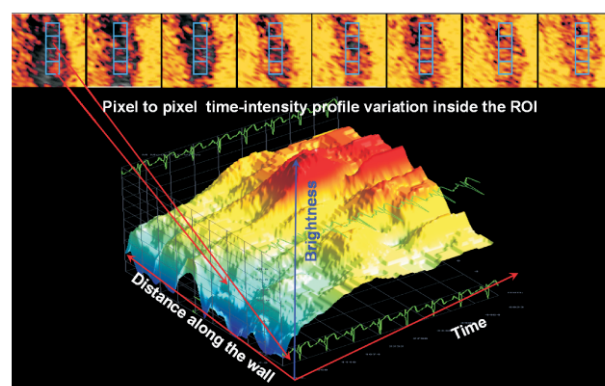


Fig. 5. Myocardial contrast signal is not homogeneous.

portions of the same areas of the septum. This is normal and is related to non-homogeneous contrast enhancement. We tried to solve this problem by averaging signal intensity into the ROI.

Yet another problem is the *first frame after the flash*. Quantitative parameters are strongly affected by residual noise remaining in the myocardium after the flash. Careful attention has to be paid to reducing the gain or increasing the flash duration so as to destroy all bubbles. Nevertheless, there are some places in the myocardium in which the constructed curve can be completely different depending on ROI location. For this reason we introduced the concept of the physiological filter, trying to avoid all the problems related to the noise inside the myocardium after the flash.

Qontrast®: Experimental validation

The Qontrast® software has been tested on 5 large white pigs at the Bracco Research Laboratories in Geneva⁴⁰. Using several ultrasound instruments in

Echographic machine	Philips Sonos 5500		Philips HDI5000		Acuson Sequoia		Esaote Megas
Software version	Rev D		10.5		7.01		1.3
Probe	S3		P4-2		3V2c-S		PA 230E
Imaging mode	PM	HA	PI	PPI	CCI	CPS	CnTi
Transmit frequency	2.5 MHz	1.7 MHz	1.7 MHz	1.7 MHz	CA3.5 MHz	P2.0MHz	1.7 MHz
Mechanical Index	0.1	0.1	0.08	0.13	0.14	0.07	0.09
Frame Rate	25 Hz	17 Hz	23 Hz	23 Hz	19 Hz	23 Hz	20 Hz
PRF	-	-	-	2500 Hz	-	-	5600 Hz
Destruction frames	2	2	4	4	manual timing	manual timing	4
Compression setting	-	-	150 dB/C3	150 dB/C3	83 dB	83 dB	-
Parameters	2/0/A/T3	2/0/A/S1/E	2DOpt: PIPen	Flow Opt: C-Res	S2/+1/0/0 $\Delta=2$	S2/0/1/0 $\Delta=2$	PST 10/2

Fig. 6. Experimental protocol - ultrasound equipment.

the same pig, different low-MI contrast modalities were compared; fluorescent microspheres were used as a reference method. The animals were anesthetized by isoflurane inhalation (Forène 1.5% in air/O₂) and pentobarbital infusion (5 ml/h). Four catheters were inserted into the vessels of the animals: one into the femoral artery for the collection of reference blood samples during fluorescent microsphere injections, one into the femoral vein for the infusion of pentobarbital, one into the right external jugular vein for microbubble infusion, and one into the left atrium for injection of fluorescent microspheres. The left anterior descending coronary artery (LAD) was dissected free from surrounding tissue, a blood-flow sensor was placed snugly around the vessel, and different degrees of stenosis were induced by a custom-designed inflatable balloon. The animals were then given an infusion of sulphur hexafluoride microbubbles (SonoVue®, 1 ml/min) by the basculating pump Viewject⁴¹. At steady state, 2 minutes after starting the infusion, 2 flash sequences were acquired manually at an interval of at least 25 s. Imaging sequences were obtained at baseline, at 50% stenosis and at 100% stenosis (i.e. occlusion). Fluorescent microspheres were injected at each level of stenosis as "gold standard". The image sequences were repeated four times using different US equipment (i.e. Philips Sonos 5500, Philips HDI5000, Acuson Sequoia and Esaote Megas; see further details in Fig. 6). An example of how the parametric images follow the flow in the area of interest directly is provided in Fig. 7. A close correlation was found between the ratio risk area/control area (MBF) by microspheres and the equivalent ratio risk area/control area ($SI \times \beta$) by MCE, being approximately 0.9 for any contrast modality

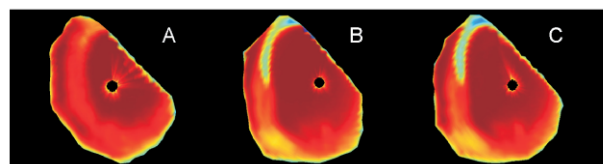


Fig. 7. Parametric imaging.

tested (Fig. 8). In conclusion, experimental data strongly support the clinical use of *Qontrast*[®].

Qontrast[®]: clinical validation

We have generated preliminary clinical data comparing parametric MCE and SPECT in 12 patients with recent myocardial infarction. The clinical trial was performed in compliance with the tenets of the declaration of Helsinki; the trial was approved by the local Ethics committee and all patients had given their written informed consent before undergoing echocardiography.

Microvascular damage was evaluated by real-time MCE using continuous infusion of SonoVue by Viewject. At this time, SonoVue® is one of the most promising contrast agents when used with low-MI techniques, for the following characteristics: it is highly responsive to ultrasound energy, it can easily be destroyed at high energy, and the harmonic signal at low energy is strong. This contrast agent was administered as an infusion of 120-240 ml/h (2-4 ml/min) using Sonos 5500 (Philips) or CnTi (Esaote) and real-time color and grayscale imaging (rt-MCE). Myocardial perfusion was assessed using a 16-segment model (4-2-chambers apical views for rt-MCE, and horizontal and vertical long axis views for SPECT). A total of 119 segments were evaluated by both methods. For each LV segment, MCE-derived quantitative parameters

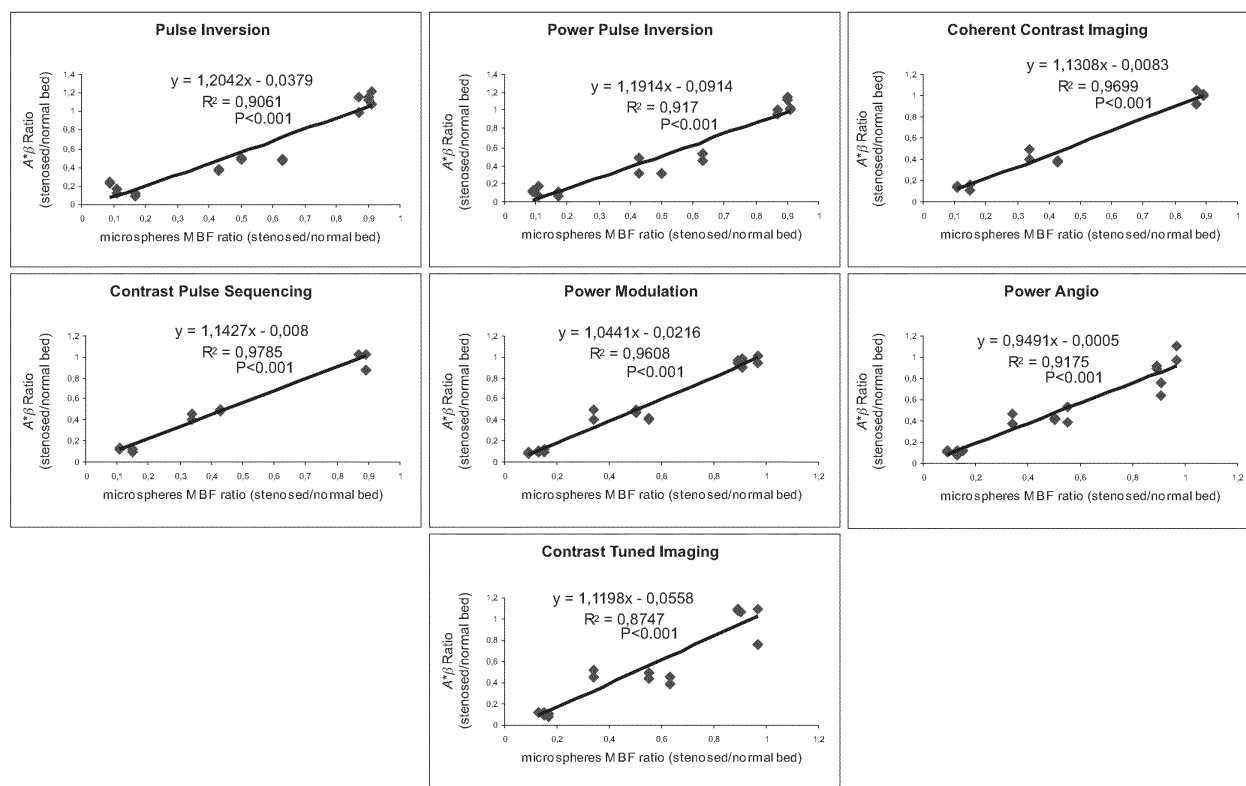


Fig. 8. Contrast modalities.

(peak SI and $SI \times \beta$) were calculated. Receiver operating characteristics (ROC) curve analysis was employed to determine the optimal cut-off values for both parameters to differentiate between normal and abnormal SPECT perfusion imaging. The best cut-off value was >14.3 l/s for peak SI and >7.9 l/s for $SI \times \beta$. Applying these values, the agreement between both techniques was 83% with a kappa value of 0.53 for peak SI and 83% with a kappa value of 0.55 for $SI \times \beta$. The sensitivity and specificity of peak SI to detect abnormal segmental tracer uptake at rest were 67% and 88%, respectively, whereas for $SI \times \beta$ these were 70% and 87%, respectively. Thus, satisfactory agreement was found between these two perfusional methods. Since this is one of

the first studies⁴² trying to compare quantitative MCE-derived parameters with SPECT perfusion imaging, we used the latter technique as a gold standard. However, SPECT may not be considered as a perfect reference method due to the high incidence of false positive perfusion defects. An higher incidence of perfusion abnormalities was detected in segments with normal wall motion by SPECT as compared to quantitative MCE. Further, parametric MCE produces much more information than SPECT, providing data not only on myocardial blood volume but also on myocardial blood flow velocity, whereas SPECT provides information on blood volume only (Fig. 9). The mean differences between these two perfusional methods are summarized in Fig. 10.

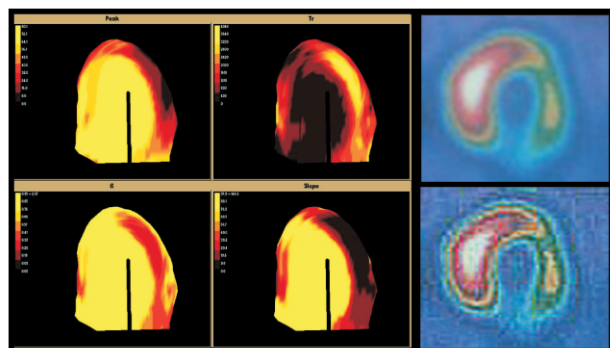


Fig. 9. Patient 65 y/o: Volume + velocity.

Another important feature is the ability of parametric MCE to detect and analyze large-area perfusion defects (Fig. 11) as well as small areas of hypoperfusion in greater detail than SPECT, as shown in the case of a 56-year old man with

MCE vs SPECT

Estimate of relative differences in tracer distribution in different areas	SPECT
Direct estimate of myocardial perfusion	MCE
Simultaneous visualization of perfusion and contraction	MCE
Partially cellular metabolism dependent	SPECT
Pure perfusion tracer	MCE

Fig. 10. MCE vs SPECT.

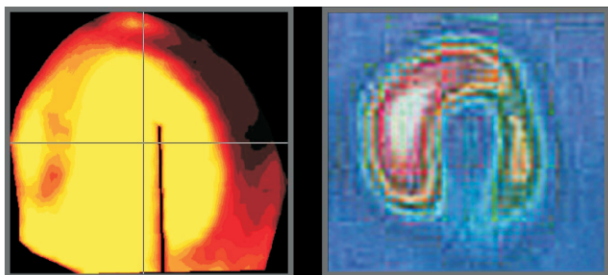


Fig. 11. Patient 65 y/o: Extensive lateral defect.

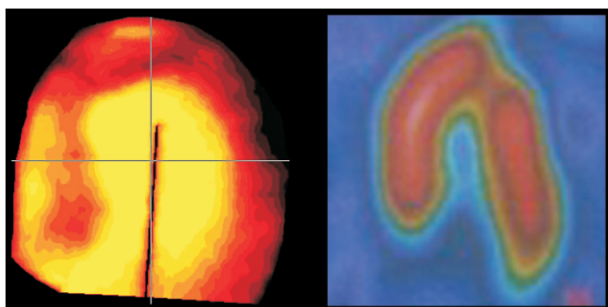


Fig. 12. Patient 65 y/o: Apical hypoperfusion.

a previous apical infarction and a residual small apical hypoperfusion (Fig. 12).

Conclusion

In conclusion, parametric MCE is a promising imaging technique for the assessment of myocardial perfusion in patients with suspected or known coronary artery disease. At present the use of MCE-derived quantitative parameters should be tested in large trials to assess the additional value as compared to qualitative information in different clinical settings such as acute myocardial infarction and stress testing.

The successful exploitation of the full potential of MCE in clinical practice will depend on a number of factors, including usage of quantitative analysis to produce strong clinical evidence of its usefulness, development of guidelines for its application by scientific Societies, inclusion in the NHS reimbursement list, local availability of equipment with "contrast capability", and approval of usage of contrast media in the indication of myocardial perfusion by the regulatory health authorities.

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