Real-time three-dimensional myocardial contrast echocardiography: is it clinically feasible?

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Aims Real-time 3D echocardiography (RT3DE) and 2D low mechanical index (LMI), contrast specific, myocardial perfusion imaging are now both accepted techniques. We evaluated the feasibility of an RT3DE LMI implementation in unselected patients.

Methods and results Forty-six patients undergoing contrast enhanced dobutamine stress echo were imaged with novel 3D LMI power modulation software. All patients underwent contrast enhanced 2D and RT3DE acquisitions, in left ventricular opacification (LVO), and LMI perfusion modes. The data sets were evaluated segmentally for wall motion (WM) and myocardial contrast enhancement. Of the 736 evaluated segments, WM could be assessed in 726 (98.6%) of the 2D and 708 (96.2%) 3D segments (P = 0.007). Perfusion could be assessed in 721 (98%) of 2D and 701 (95.2%) of 3D segments (P = 0.006). Six hundred and sixty-one segments had normal WM and thickening in 2D and of these RT3DE demonstrated normal myocardial opacification in 77.2% of basal, 85% of mid, and 91.8% of apical segments. Thirty-four segments were akinetic, with no evidence of perfusion in 2D, and of these RT3DE revealed a perfusion defect in 31 (91%, P = NS).

Conclusion LMI RT3DE evaluation of myocardial perfusion is feasible in most segments. It has the potential to accurately locate and possibly quantify perfusion defects.

KEYWORDS
3D echo; Contrast; Myocardial perfusion

Background
Over the years, trans-thoracic echocardiography has proved to be a very powerful and safe tool in the non-invasive assessment of cardiac conditions, and is indispensable in a modern day cardiac department.

Advancements in technology, of both image acquisition and analysis, have offered improved capabilities, and even new modalities, which have hugely increased the indications and applications of echocardiography. Arguably, two of the most important of these advancements have been intravenous contrast agents, for left ventricular opacification (LVO) and myocardial perfusion [using low mechanical index (LMI) imaging], and real time three-dimensional echo (RT3DE).

A promising new technology is the combination of these modalities to offer real-time three-dimensional myocardial contrast echocardiography (RT3DMCE); however, its feasibility and clinical role are yet to be determined.

In order to evaluate the feasibility of RT3DMCE, in a clinical setting, we employed a novel 3D LMI power modulation software package in the assessment of unselected patients.

Patient population
A total of 46 (24 male) consecutive patients referred to our department for dobutamine stress echocardiography (DSE) were included. All patients were referred for DSE for standard reasons and all required contrast enhancement on clinical grounds. One patient was excluded because of sub-optimal images despite contrast infusion. Their median age was 69 (mean 67.5) with a range of 49–82.

The majority of patients (30) were under investigation for chest pain. The most common cardiovascular risk factor was hypertension followed by dyslipidaemia and then diabetes (Figure 1).

Methods
All the patients were scanned by the same experienced operator, using a Philips IE33 system (Philips Medical Systems, Bothell, WA, USA), equipped with novel 3D LMI power modulation software.
Standard LMI contrast enhanced 2D views were taken at baseline (apical four chamber, two chamber, and parasternal long axis and short axis) with an S3-1 transducer.

Then, two real-time 3D data sets were acquired over seven cardiac cycles, with a breath hold, using an X3-1 transducer: first, in LVO mode with a mechanical index (MI) of 0.24 and then in LMI perfusion mode with an MI of 0.14.

Gain settings were adjusted carefully so that prior to contrast administration there was minimal background tissue signal. Three-dimensional data sets were stored digitally on DVDs and subsequently analysed off-line using Qlab software (Philips, Andover, MA, USA). Frame rates achieved were just under 20 Hz for LVO and 15 Hz for LMI perfusion mode.

A number of techniques were used to analyse the 3D data sets. These included manual cropping techniques to visualize each segment and Qlab presentation aids such as the multi-plane reconstruction (MPR) viewer (Figure 2).

Three-dimensional analysis was done by an independent analyser who was blinded to the 2D results. Two months after the first analysis, 10 data sets were randomly selected for rereanalysis. This was done by the original analyser and one other in order to obtain inter and intra-observer variability.

The contrast agent used in all patients was SonoVue (Bracco, Milan, Italy)1,2 at a continuous infusion of 0.7–0.9 ml/min via an infusion pump. The infusion rate was adjusted if necessary to obtain maximum LVO (in both modes) without attenuation. Contrast doses were the same for both 2D and 3D data set acquisitions and infusion rates were managed in an identical fashion. SonoVue’s safety and efficacy for LVO has been proven3 and it has a licence in many countries for this application. However, despite a number of studies successfully utilizing it for myocardial perfusion assessment,4–7 it is not currently licensed for this.

During data set analysis, the left ventricular walls were divided using the standard American Society of Echocardiography 16 segment model:8 six basal, six mid, and four apical, and each segment was assessed individually in a semi-quantitative fashion for wall motion (WM) and perfusion.

The 2D segments were scored for WM and perfusion (contrast opacification) and the 3D segments were assessed for WM in the LVO mode and the amount of myocardial opacification seen relative to the LVO setting was assessed in LMI mode (Figure 3).

Each segment was evaluated for the presence of normal, hypokinetic, or akinetic WM and, in addition the number of segments inadequately visualized was recorded.

With regards to perfusion, each segment was evaluated for the presence of homogenous myocardial opacification, patchy opacification, or an absence of opacification. Once again the segments that were inadequately visualized were recorded.

Statistical analysis

All statistical analysis was done using the commercially available JMP software package (SAS Institute, Cary, NC, USA). Paired t-tests were used to compare results between 2D and 3D and statistical significance was taken at P < 0.05. Inter and intra-observer agreements were calculated as percentages and kappa (κ) values. Kappa > 0.8 was taken as excellent agreement, >0.5 as a good agreement, and <0.3 being poor.

Results

A total of 736 left ventricular segments were imaged using both modalities. During assessment of the 2D images, WM could be assessed in 98.6% (726) of the segments. Six hundred and sixty-one of these had normal WM and thickening. Thirty-one segments were hypokinetic and 34 akinetic.

With regards to perfusion, 98% (721) of the 2D segments could be assessed. The main reason for inability to assess
was inadequate visualization secondary to poor penetration, rib shadow, or contrast attenuation.

During evaluation of the 3D data sets, WM could be assessed in 96.2% (708) of the segments and perfusion in 95.2% (701). When the number of adequately visualized segments was compared between 2D and 3D, the differences were statistically significant ($P = 0.007$ for WM and $P = 0.006$ for perfusion), demonstrating that 2D echo is better than 3D with regards to the number of segments that can be adequately visualized. Nevertheless, there was a good agreement for segment visualization between 2D and 3D, with 97.6% for WM ($\kappa = 0.52$) and 97.4% for perfusion ($\kappa = 0.61$) (Figure 4).

On evaluation specifically of WM abnormalities, there was excellent agreement between 2D and 3D: 93% for apical segments, 93.5% for mid, and 94% for the basal.

Assessment of perfusion defects revealed an agreement of 78% in the apical segments, 71% in the mid segments, and 64% in the basal segments. The total was 70%, indicating fair agreement overall (Table 1).

Out of the 661 segments that had normal WM, thickening, and perfusion in 2D, normal 3D myocardial opacification was seen in 91.8% (149) of apical, 85% (212) of mid, and 77.2% (193) of basal segments. This made a total of 83.8% (554) (Figure 5).

Thirty-four segments were both akinetic and had no evidence of perfusion in 2D. Of these segments, RT3DMCE...
successfully demonstrated a perfusion defect (marked as either absent or patchy perfusion) in 31 (91%, \( P = \text{NS} \)) (Figure 6).

None of the patients experienced any adverse side effects during, or immediately after the studies.

Intra and inter-observer agreements were good for all comparisons. For 3D WM, these were 90.9% (\( k = 0.61 \)) and 82% (\( k = 0.57 \)) and for 3D perfusion were 78% (\( k = 0.56 \)) and 75% (\( k = 0.51 \)), respectively.

**Discussion**

The technology we employed is a successful combination of two of the most important recent developments in echocardiography, each having already made very different contributions to the field.

First, the use of ultrasound contrast offers improved endocardial border definition at rest, and stress, therefore enhancing diagnostic accuracy. It also allows assessment of patients who would not normally be suitable due to poor imaging windows.

Furthermore, these contrast agents now offer visualization of tissue perfusion.9 The use of contrast with LMI and power Doppler imaging is moving out of the research arena and can offer safe and accurate assessment of myocardial perfusion.10 It has the ability to reveal resting perfusion defects in those with known coronary artery disease,11 and has been shown to be comparable in accuracy to positron emission tomography,12 the current gold standard for perfusion imaging. Its use during stress enhances diagnosis, offers prognostic information,13,14 and it may have the potential to become the diagnostic test of choice for both reversible ischaemia and viability.15

Secondly, RT3DE is a safe and quick bedside test that provides accurate and reproducible left ventricular volume measurements, when compared with cardiac magnetic resonance imaging.16 Three-dimensional dyssynchrony analyses have been shown to be valuable in the assessment of patients for cardiac resynchronization therapy,17 and it has also been successfully used in the diagnosis of structural heart disease and in the assessment of left ventricular remodelling.18,19

Studies have already been done proving the feasibility of RT3DE during contrast enhanced stress echo (for LVO), documenting its accuracy and potential to speed up such examinations.20-23

There has also been work done with myocardial perfusion and 3D echo, using both reconstructed and real-time 3D.24-29 These studies have assessed accuracy, feasibility, and even contrast quantification. However, they have predominantly examined animal models or healthy volunteers, although more recently Iwakura et al.30 have successfully employed it in patients, using intra-coronary contrast.

The purpose of our study was to examine the feasibility of this relatively new technology in the setting of a clinical echo exam. As might be expected because of differences in spatial resolution, 2D echo offers slight superiority to 3D for segment visualization. Some segments, in particular the basal ones, offer more of a challenge when it comes to image acquisition and analysis, but this stands true for contrast echocardiography in general. As image acquisition continues to improve so too will this. Agreement between WM analysis in the two methods is very good and perfusion analysis, although not quite as good is still fair.

In future, this technology could be used to accurately locate, and even quantify (using 3D volume quantification techniques), myocardial perfusion defects. It may also reduce the time necessary for such studies as four image acquisitions could be replaced by one, with cropping done offline after the patient has left the department. Although we analysed WM and perfusion in separate datasets, the two can be analysed simultaneously, in the LMI setting, in a similar manner to that used in 2D contrast echocardiography. This may further speed up analysis time. However, as with 2D if these are done simultaneously frame rates are lower than when acquiring just LVO data sets.

Not only could this technology be used to document resting perfusion defects, it also has the potential to give valuable functional information when used in conjunction with stress. Currently, frame rates at peak (<10 Hz) hinder accurate analysis during the later stages of dobutamine stress, but this would not be such an issue with vasodilator protocols, which induce less of a chronotropic effect.

**Limitations**

A significant limitation to the study is the assumption of 2D echo as a gold standard, particularly for perfusion imaging.
Also the majority of the segments we assessed were normal. Now that we have demonstrated the feasibility of RT3DMCE, in a clinical setting, further studies with a greater number of defects are warranted and comparison with visualization of coronary anatomy (i.e. angiography) and alternative perfusion techniques would help delineate a clinical role.

A quantitative assessment of the 3D data sets is not currently available and as a result our analyses were done in a semi-quantitative fashion. The X3-1 3D transducer is currently not able to emit a destructive flash so our assessments were limited to myocardial blood volume and could not include myocardial blood flow. Quantitative perfusion assessment would be a valuable addition to this technology and would facilitate comparison with other more widely used techniques.

Side-by-side analysis of LVO/perfusion data sets is not currently possible and could be a useful addition to the software, possibly enhancing accuracy.

Finally, it is unknown if spatial resolution will limit the ability to visualize small or subendocardial defects.

**Summary**

Real-time three-dimensional myocardial contrast echocardiography is feasible in the majority of left ventricular segments at rest. Perfusion can be assessed reliably in normal segments and larger perfusion defects can be visualized. In future, 3D quantification techniques could be used to accurately measure the volume of perfusion defects.

**Conflict of interest:** M.J.M., A.B., S.K. and B.S.R. are on the speakers bureau for Philips Medical Systems.

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**References**