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Analysis of regional wall motion during contrast-enhanced dobutamine stress echocardiography: effect of contrast imaging settings

Bernard Cosyns[1]*, Guy Van Camp[1], Steven Droogmans[1], Caroline Weytjens[1], Danny Schoors[1], and Patrizio Lancellotti[2]

[1]*Cardiology Department, UZ Brussel, Vrije Universiteit van Brussel, Laarbeeklaan, 101, B-1090 Brussels, Belgium; and*
[2]*Cardiology Department, CHU Sart Tilman, Université de Liège, Belgium*

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Aims Myocardial contrast perfusion echocardiography (MCE) allows simultaneous assessment of perfusion and function. However, low frame rate during MCE may reduce the viewer's ability to discern contractile dysfunction. This study sought to compare MCE and left ventricular opacification (LVO) settings with regard to wall motion abnormalities (WMA) at rest and during dobutamine stress echocardiography (DSE).

Methods and results In 50 patients scheduled for coronary angiography and with poor baseline image quality, MCE and LVO were performed during DSE. Regional wall motion was assessed and inter-observer agreement was determined for each imaging modality. The endocardial border score index was similar for both modalities. The wall motion score index (WMSCI) at peak stress using MCE was well correlated with WMSCI obtained with LVO ($r^2 = 0.9$, $P < 0.001$). However, WMSCI at peak stress was underestimated by MCE (1.66 ± 0.58 with DSE-LVO vs. 1.535 ± 0.50 with DSE-MCE; $P < 0.001$). Inter-observer agreement on the presence of WMA was 0.65 for MCE and 0.67 for LVO at peak stress.

Conclusion Myocardial contrast perfusion echocardiography provides equal endocardial border delineation compared with LVO modality. Although the inter-observer agreement is slightly higher with LVO compared with MCE, it is not significantly different with MCE at peak stress. Despite the similar improvement in endocardial border delineation, LVO settings allow the detection of more WMA than MCE at peak stress, leading to a significantly higher accuracy for the detection of ischaemia in patients suspected of coronary artery disease when only wall motion is taken into account.

Introduction

Using echocardiography, the most current way to get insight into the effect of coronary artery disease (CAD) on the left ventricular (LV) myocardium is the analysis of regional systolic function. Stress echocardiography is an established clinical tool with a high sensitivity and specificity for the diagnosis of CAD. It is based on the detection of wall motion abnormalities (WMA) and thus requires visualization of all myocardial segments to document or exclude abnormalities definitively. Moreover, stress echo, which provides an indirect marker of hypo-perfusion by recognition of WMA, has limitations owing to subjective interpretation, reader variability, and dependence on the induction of ischaemia.

* Corresponding author. Tel: +32 496468501; fax: +32 2 387 30 65.
E-mail address: bcosyns@skynet.be

Contrast echocardiography has been shown to improve endocardial border definition, wall motion scoring, and reproducibility at rest and during stress.[1–6] In the ischaemic cascade, hypoperfusion precedes WMA.[7] Theoretically, a clinical method to directly assess the perfusion should be more sensitive and there is also a clear role for contrast echocardiography to assess myocardial perfusion at rest and during stress.[8–10] Low power imaging has been proposed as ideal technique for allowing assessment of myocardial perfusion and wall motion simultaneously. However, the application of low power imaging in clinical practice potentially causes additional limitations regarding wall motion evaluation because of artefacts and lower frame rate.[11,12] A recent study has shown that myocardial contrast perfusion echocardiography (MCE) is inferior to left ventricular opacification (LVO) with regard to visualization of all segments and with regard to inter-observer agreement at rest.[13]

To note, contrast echo techniques for LVO have, however, essentially been performed in patients with poor image quality, whereas MCE techniques have often excluded these patients.[14] Since low frame rate during MCE may reduce the viewer's ability to discern contractile dysfunction, the objective of the present study was to compare LVO with MCE techniques during stress echocardiography, in patients with poor image quality at baseline, with regard to endocardial border definition, to adequacy of wall motion scoring, and to inter-observer agreement.

Methods

Study population

We prospectively enrolled 62 consecutive patients with poor image quality (5 or more segments unevaluable with harmonic imaging) scheduled for coronary artery angiography for suspicion of CAD. Among these, 12 patients were excluded (5 for atrial fibrillation, 3 patients with congestive heart failure and haemodynamic instability, 2 for recent (<1 month) acute myocardial infarction, and 2 refusing to participate to the study. The patient clinical characteristics of the 50 remaining are listed in *Table 1*. LV ejection fraction was obtained by conventional 99m Tc-sestamibi-gated SPECT measurements. This study was approved by the institutional review board and written informed consent was obtained.

Study design

All patients underwent rest echocardiography and dobutamine stress echocardiography (DSE) with contrast. The contrast-enhanced imaging was performed using pre-defined LVO settings (low mechanical index <0.5, gain 60%, compression 15%) that were optimized for endocardial border delineation and MCE settings (very low mechanical index <0.2, gain 60%, compression 15%) adapted to assess optimal myocardial perfusion visualization in random order, immediately after each other.

Contrast injection protocol

All patients had resting images from the parasternal long- and short-axis and apical two- to four-chamber views using harmonic imaging (Vivid 7 imaging device; GE Healthcare, Little Chalfont, UK). The commercial available contrast agent, Sonovue® (Bracco Diagnostics, Inc.), is an aqueous suspension of stabilized SF_6 microbubbles. The size of these microbubbles is between 1 and 10 μm, and their number is between 2×10^8 and 5×10^8 per mL. The solution was prepared according to the manufacturer's instructions and injected using a dedicated pump (Bracco, Italy) at an initial rate of 0.5 mL/min. The rate of infusion was adapted for optimal visualization of endocardial border definition. At peak dobutamine, a second set of contrast-enhanced images were obtained.

Table 1 Baseline characteristics

Age (years)	69 ± 13
Male gender	25 (50%)
Body surface area (m^2)	1.92 ± 0.3
LV ejection fraction	51 ± 16%
Chronic pulmonary disease	8 (16%)
Risk factors	
Smoking	22 (44%)
Hypertension	20 (40%)
Diabetes mellitus	15 (30%)
Prior revascularization	8 (16%)
Prior myocardial infarction	6 (12%)

Dobutamine stress echocardiography

DSE was performed using a standard protocol of dobutamine administration (10, 20, 30, 40 μg/kg/min every 3 min+0.25 mg atropine every minute with a maximal dose of 1 mg if the target heart rate was not reached). Beta-blockers were discontinued for 36 h prior to the study. A digital online system with ECG-driven cineloop representation was utilized for recording images. Digitized cineloops were compared side by side before and after dobutamine administration in a quad screen format and were analysed offline by the cardiologist, using the EchoPAC software (GE Vingmed, version 3.1.3). The electrocardiogram was monitored continuously. A 12-lead electrocardiogram and blood pressure records were performed at each step and during the recovery phase. Causes of premature arrest were the target heart rate (>85% of the predicted maximal heart rate), a blood pressure ≥220/110 mmHg, fall in systolic blood pressure ≥20%, angina, ST depression ≥2 mm, severe arrhythmias, intolerance, and myocardial ischaemia (new or worsening WMA by ≥1 grade in two or more contiguous segments). Myocardial perfusion images were not taken into account for stopping the test.

Image analysis

The regional wall motion was analysed in slow motion as a standard, using a 16-segment model and a conventional scoring system according to the American Society of Echocardiography. A score was obtained for wall motion as 1, normal; 2, hypokinetic; 3, akinetic; 4, dyskinetic, and unable to interpret,[15] and a WMSCI was calculated by dividing the total score with the number of evaluated segments. A mean endocardial border visualization score index was also calculated as the number of evaluable segments divided by the total number of segments. Analysis of the same echocardiography was performed offline, in random order and blinded of the results for the other modalities and coronary artery angiography.

Coronary angiography

All patients underwent coronary artery angiography within 48 h after DSE examinations. Coronary angiography was performed by the femoral approach, with the modified Seldinger technique. Angiograms were reviewed by experienced angiographers for calculation of per cent stenosis. The angiographer was blinded to the DSE results. Significant CAD was considered present when any one of the major epicardial coronary arteries or one of their major branches had >50% stenosis by quantitative analysis (QCA-CMS system® (MEDIS Medical Imaging Systems, Leiden, The Netherlands).

Statistics

Data were expressed as mean ± SD. Continuous variables were tested by Student's *t*-test, and nominal findings were analysed by a Fisher's exact test. Overall agreement of WMA interpretation by patient and segment between blinded observers (B.C. and G.V.) was identified for both modalities at baseline and at peak test. Average coefficients of agreement (κ) were computed between observers. The κ-test was used to test the hypothesis that agreement was greater than chance alone and was graded as described previously.[16] Linear regression analysis was applied to calculate the correlations between wall motion score index (WMSCI) obtained with both echo modalities at peak stress and was assessed with the Spearman coefficient. Calculations of sensitivity, specificity, and diagnostic accuracy of DSE-LVO and DSE-MCE for the detection of CAD were performed with reference to cardiac angiogram results (a correlation between WMA and a significant stenosis of the corresponding coronary artery was considered as true positive). Differences in sensitivity, specificity, and accuracy were compared using McNemar test. A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS (version 14.0) statistical software (SPSS Inc., Chicago, IL, USA).

Results

All patients underwent stress contrast echocardiography without any major side effects. The maximal dose of dobutamine was 35.2 ± 8.5 μg/kg/min. Atropine administration was required in six patients. Heart rate (70 ± 10 and 136 ± 17 bpm) and systolic blood pressure increased significantly from rest to peak stress (128 ± 29 and 175 ± 40 mmHg) ($P < 0.001$). The mean frame rate was lower with MCE than with LVO (32 ± 5 and 67 ± 7 images/s, respectively; $P < 0.0004$), at rest, and at exercise. Significant CAD was detected in 30 patients, 9 had single-vessel disease, and 21 presented multivessel disease. Twenty-two had left anterior descending artery lesion (73%), and 11 had circumflex or right coronary artery lesions (37%). There was no significant CAD in 20 subjects.

Endocardial border definition

As depicted in *Figure 1*, there was no significant difference between LVO and MCE technique for endocardial border delineation at rest (mean endocardial border score index: 0.92 ± 0.15 vs. 0.91 ± 0.17; $P =$ NS) and at peak DSE (0.89 ± 0.17 vs. 0.86 ± 0.19; $P =$ NS). To note, basal segments were in general more difficult to visualize with both methods.

Adequacy of wall motion scoring

WMSCI was similar for both imaging modalities at rest (1.28 ± 0.5 with LVO vs. 1.26 ± 0.49 with MCE; $P =$ NS). Although the WMSCI at peak stress using LVO was well correlated with WMSCI obtained with MCE ($r^2 = 0.9$, $P < 0.0001$) (*Figure 2*), WMSCI at peak stress seemed to be an underestimate with MCE (1.66 ± 0.58 with DSE-LVO vs. 1.535 ± 0.50 with DSE-MCE; $P < 0.001$). The proportion of normal segments at baseline scored as abnormal at peak stress was not significantly different with both methods. The proportion of new wall abnormalities was similar with both LVO and MCE settings according to the location of the WMA.

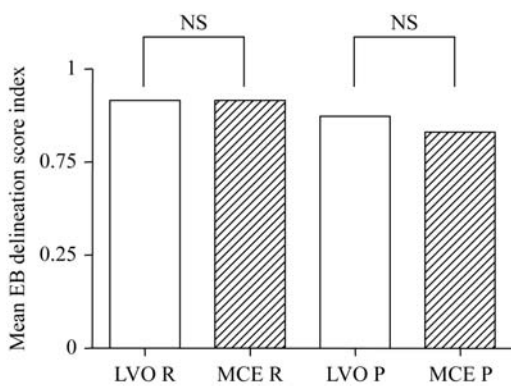

Figure 1 Improvement in endocardial border (EB) delineation at rest (R) and during peak dobutamine stress echocardiography (P) using of contrast with left ventricular opacification (LVO) and with myocardial contrast perfusion echocardiography (MCE).

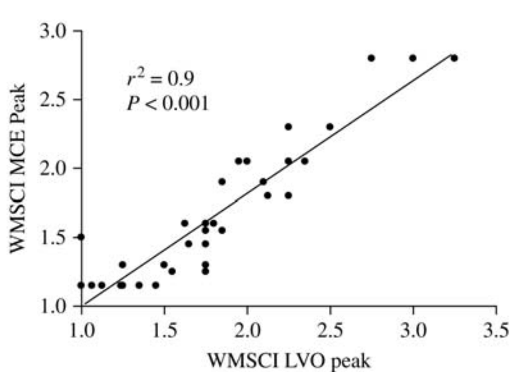

Figure 2 Correlation between wall motion score index (WMSCI) obtained with left ventricular opacification (LVO) and with myocardial contrast perfusion echocardiography (MCE) at peak stress dobutamine.

Inter-observer agreement

At rest, the examinations were identically interpreted between observers with LVO ($\kappa = 0.87$) and MCE ($\kappa = 0.86$). In case of WMA, the inter-observer agreement remained fairly good for both methods at peak stress (0.67 for LVO and 0.65 for MCE).

Sensitivity and specificity of the test for coronary artery disease

Sensitivity and specificity for the detection of CAD are depicted in *Table 2*. Sensitivity of DSE was higher with LVO (88%) than with MCE (78%; $P < 0.05$) in the overall population and in patients with multivessel disease (90 vs. 76%, $P = 0.04$). Conversely, there were no significant differences in respect of specificities (91 vs. 86%, NS).

Discussion

The present study demonstrates that during DSE, MCE provides similar endocardial border delineation compared with LVO modality in patients with bad quality imaging at baseline. However, the LVO modality provides higher accuracy than MCE for detecting CAD throughout changes in wall motion. Such a difference was not related to difficulties in the interpretation of the test with MCE since the inter-observer agreement between experienced readers was similar for both techniques at rest and at peak stress.

Usefulness of left ventricular opacification for detecting abnormal wall motion

Semi-quantitative assessment of regional function, incorporating endocardial wall motion and thickening, is the most common approach to evaluate regional myocardial wall abnormalities.

Although 2D echocardiography is the method of choice for these assessments, the accuracy and reproducibility of this technique have significant limitations.[17–19] Some of the inaccuracy of 2D echocardiography pertains to suboptimal image quality. The use ultrasound contrast agents for LVO

Table 2 Sensitivity and specificity of left ventricular opacification and myocardial contrast perfusion echocardiography during dobutamine administration for detecting coronary artery disease

	LVO	MCE	*P*-value
Overall population (%)			
Sensitivity	88	78	0.045
Specificity	91	86	0.09
Accuracy	90	84	0.047
Single-vessel disease (%)			
Sensitivity	78	73	0.1
Multi-vessel disease (%)			
Sensitivity	90	76	0.04

LVO, left ventricular opacification echocardiography; MCE, myocardial contrast echocardiography.

have been shown to improve endocardial border detection and, therefore, the accuracy of conventional 2D echocardiography for the assessment of LV volumes, LV function, and regional wall motion[1,3,20] to a level comparable with magnetic resonance imaging (MRI). As a result, the inter-observer reproducibility of LVO reached the high inter-observer agreement of MRI.[3] During stress, reduced endocardial border definition is exacerbated because of chest wall movement during hyperventilation and cardiac translational movement during tachycardia. With fundamental imaging, inadequate endocardial border definition has been reported in up to 30% of patients undergoing stress echocardiography. It is well proved that suboptimal images altered the reproducibility of 2D stress echocardiography and the inter-observer variability. In this situation, the reported inter-institutional institutional observer agreement has been shown to be as low as 43%.[21] As we found, contrast-enhanced echocardiography for LVO increased the accuracy and reproducibility of regional wall motion assessment during stress.[4,22]

Accuracy of myocardial contrast perfusion echocardiography for detecting abnormal wall motion

Myocardial perfusion imaging is a different approach to get insight into the effect of CAD on the LV myocardium (induce perfusion defects during stress testing). Myocardial contrast perfusion echocardiography with low-power ultrasound allows the simultaneous evaluation of WMA and perfusion abnormalities. In the absence of prior infarction, the detection of CAD on myocardial perfusion imaging is based on the occurrence of reversible perfusion defects during pharmacological or exercise stress. A recent meta-analysis has shown an overall superiority of MCE to nuclear imaging for the detection of CAD.[23] During DSE, the sensitivity of MCE has also been shown to be higher than that of wall motion at both maximal and intermediate doses.[24–26] Previous studies have reported a low specificity for perfusion MCE for the detection of CAD.[24–26] Moreover, MCE may be severely affected by image quality. However, patients with poor image quality are often excluded from perfusion imaging studies. There is also a lack of data regarding the impact of MCE settings for the evaluation of WMA, especially during stress studies. The previously published studies using MCE settings for the analysis of WMA during stress test often compare unfavourably even with fundamental stress echo.[12] In the present study, MCE settings have provided equivalent endocardial border delineation probably resulting in the same inter-observer agreement. This is consistent with previous studies and is particularly true if the operators are in their learning phase.[27] However, this does not translate in similar accuracy for the detection of WMA and may explain the unfavourable comparison with myocardial perfusion data.[12]

Weaknesses of myocardial contrast perfusion echocardiography for wall motion analysis

High frame rate echocardiography is capable of extracting more subtle information on regional wall motion from ultrasound images that may improve the sensitivity of echocardiographic for diagnosing ischaemia. In addition to subtle changes in magnitude of wall motion, this less-readily visualized information may include altered temporal aspects of systolic LV function. Indeed, during acute ischaemia, temporal changes have been shown to occur earlier than changes in the magnitude of wall motion of induced myocardial ischaemia.[28] The use of MCE settings to detect WMA during stress echocardiography with frame rates between 25 and 30 Hz may thus decrease the ability of detecting tardokynesis as a sign of ischaemia. The application of contrast for better endocardial border delineation represents the main indication for contrast in echocardiography, is easy to perform, and does not require a specific expertise. On the contrary, perfusion analysis with MCE is much more challenging and requires training for the acquisition and the interpretation of the data.[29] Although the combination of both approaches using perfusion and function analysis for improving the accuracy of ischaemia detection with DSE is promising, the results of the present study suggest that higher frame rates are highly desired when MCE settings are used.

Limitations

We did not analyse the impact of perfusion data or the combination of perfusion data with WMA data on diagnostic accuracy of both tests. Although we did not provide perfusion data, we were aware that the reader of MCE was not completely blinded to perfusion information and that the combination of perfusion and WMA analysis might have increased inter-observer agreement. Although MCE stress requires more expertise and is more challenging for the analysis of perfusion, the analysis of wall motion during contrast-enhanced DSE is less demanding. However, in this particular study, the readers were experienced to avoid any bias.

Conclusions

Myocardial contrast echocardiography provides equal endocardial border delineation compared with LVO modality. Despite this similar improvement in endocardial border definition, LVO settings allow the detection of WMA than MCE at peak stress leading to a significantly higher accuracy for the detection of ischaemia in patients suspected of CAD when only wall motion is taken into account. Although the inter-observer agreement is slightly higher with LVO compared with MCE, the inter-observer agreement is not significantly different with MCE at peak stress. Therefore, in patients with poor quality images, the contrast settings should be taken into account for the routine analysis of wall motion during DSE.

Conflict of interest: none declared.

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