The additive value of three-dimensional derived left atrial volume and carotid imaging in dobutamine stress echocardiography

Vasileios Sachpekidis, Amit Bhan, Matthias Paul, Silvia Gianstefani, Lindsay Smith, Joseph Reiken, Nicola Walker, Derek Harries, Peter Pearson, and Mark J. Monaghan*

Department of Non-Invasive Cardiology, King’s College Hospital, Denmark Hill, London SE5 9RS, UK

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Aims
To evaluate whether the three-dimensional (3D) left atrial volume index (LAVI) and/or the presence of carotid plaques (CP) can predict the result of dobutamine stress echocardiography (DSE), thereby aiding interpretation.

Methods and results
We studied 130 patients (52 male, mean age 63 ± 11 years) with normal resting wall motion (WM) undergoing DSE. All patients had the end-systolic 2D and 3D LAVI measured, as well as bilateral carotid scanning. DSE was reported as abnormal in 50 (38.5%) patients. 3D end-systolic LAVI measurements were significantly higher (31.5 ± 8.2 vs 27.4 ± 7.4 mL/m², P = 0.004) in those with an abnormal DSE. The two groups did not differ significantly on the 2D derived maximum LAVI measurements (36.2 ± 9.5 vs 34.2 ± 11.2, P = 0.299) and the presence of plaques in the carotid arteries (89.1 vs. 76.2%, P = 0.100). Receiver operating characteristic curves were created to define cut-offs that could predict the DSE result for the 3D LAVI. A 3D LAVI of ≥24.5 mL/m² had a sensitivity of 80% for predicting an abnormal DSE, whereas a value of ≥36.0 mL/m² had a specificity of 93% for the same cause. Intra-observer (r = 0.997, P < 0.0001) and inter-observer (r = 0.961, P < 0.0001) variability for 3D LAVI measurements was found to be excellent.

Conclusion
Three-dimensional (but not 2D) assessment of LAVI may offer additional information in predicting the result of DSE. Carotid scanning did not offer additional information for the same cause.

Keywords
Stress echocardiography • 3D echocardiography • Left atrial volume • Carotid plaque

Introduction
Dobutamine stress echocardiography (DSE) is a well-validated and cost-effective test that confers not only the diagnosis of coronary artery disease (CAD), but also valuable prognostic information.1–4 Although the accuracy of DSE for detection of CAD is good, with most authors reporting overall sensitivities of 68–95% and specificities in the range of 77–97%,1 analysis is largely subjective and based upon a visual interpretation of wall motion and thickening abnormalities (WMAs). This results in a steep learning curve for the technique and significant inter- and intra-observer variability among anything other than the most experienced operators. In an attempt to overcome these problems, many novel echocardiographic techniques, such as myocardial perfusion contrast echocardiography, myocardial velocity imaging, and coronary Doppler flow reserve of the left anterior descending artery have been used. However, their value has not been well established to date.3 Therefore, it would be beneficial to discover new parameters that will increase the accuracy and reduce the subjectivity of DSE. In order to be clinically feasible and applicable, these parameters should ideally be simple, quick, and reproducible.

It has been suggested that assessment of left atrial (LA) size and/or delineation of carotid morphology may offer valuable additional information in this context; however, the exact role of these techniques is still unclear.5–7

The aim of our study was to evaluate whether the three-dimensional (3D) calculated LA volume index (LAVI)—which is LA volume corrected for body surface area—and/or the presence...
or absence of carotid artery plaque can predict a normal or abnormal DSE for reversible ischaemia in patients with no WMAs at rest.

**Methods**

**Study population**

We prospectively studied 180 consecutive patients referred to our echocardiography laboratory for DSE during a 4-month period. Exclusion criteria were defined as: patient’s refusal (1 patient), inadequate images for measuring LA volume (8 patients), inability to achieve 85% of the maximum predicted heart rate (2 patients), non-interpretable/equivocal stress test (2 patients), wall motion abnormality at rest (27 patients), moderate or severe mitral regurgitation (1 patient), a history of chronic or paroxysmal atrial fibrillation (6 patients), and chronic renal failure requiring dialysis (3 patients); due to the impact these conditions can have on the LA size.8–11

One hundred and thirty (130) patients (52 male, mean age 63 ± 11 years, range 36–87 years) were finally included in the study. Demographic data and a detailed medical history were collected for each patient. In four of these patients carotid scanning was deemed not satisfactory for interpretation; however, all other data were available for these patients and were included in the final statistical analyses.

**Dobutamine stress echocardiography protocol**

The DSE protocol that we used assesses myocardial ischaemia by graded dobutamine infusion, started with five and followed by 10, 20, 30, and 40 μg/kg/min in 3 min stages. Atropine, in doses of 0.3 mg up to a total dose of 1.2 mg, was administered intravenously as needed to augment the heart rate in patients who had an inadequate heart rate response to dobutamine. Contrast agents were used in the majority (80.8%) of patients to increase the diagnostic accuracy of the method, when baseline image quality was judged to be suboptimal. B-blockers were stopped at least 48 h before the test in all participants.

The DSE was interpreted by the same experienced examiner (M.J.M.) who was blind to the results of the 3D derived LA volume. The DSE was considered normal if the patient demonstrated normal wall motion and thickening both at rest and stress, and abnormal when WMAs (at least one segment in two views or two segments in one view) were seen during drug infusion.

**Left atrial volume data acquisition**

All echocardiographic images were obtained using an iE33 ultrasound system (Philips Medical Systems, Bothell, WA, USA). A 2D echocardiographic examination was conducted, using the SS-1 transducer, with estimation of end-diastolic and end-systolic parameters of the left ventricle, ejection fraction, as well as the LA volume using the biplane area-length method.12

A real-time 3D echocardiographic (RT3DE) examination was also performed with the X3-1 matrix-array transducer for acquisition of full-volume real-time data sets over four consecutive cardiac cycles, with suspended respiration. Careful attention was paid to depth, gain, and line density settings in order to maximize image quality. Both 2D and 3D data sets were acquired at baseline before the infusion of contrast. The RT3DE data were digitally stored on DVDs and analysed off-line using a dedicated 3D LA volume analysis package (TomTec, Gmbh). This software utilizes semi-automated border tracking to detect the endocardial surface throughout the cardiac cycle and re-creates a mathematical model of the entire chamber, from which the volume is derived.13

The maximum (end-systolic) LA volume was obtained for each patient (Figure 1). For both 2D and 3D data sets the LA volume was measured at the end of ventricular systole just before the opening of the mitral valve. Special care was taken so that the pulmonary veins and LA appendage were excluded from our calculations. All 2D and 3D derived maximum LA volumes were indexed for body surface area (LAVI). The time required for both 2D and 3D LA volume calculations was measured. Finally, for 20 randomly selected patients 3D LAVI measurements for intra- and inter-observer variability were tested.

**Statistical analysis**

Results are presented as mean values ± SD for continuous variables and as frequency percentages for categorical variables. T-test and Fisher’s exact test were used for the comparison of continuous and categorical variables, respectively. On the basis of the results of the univariable analysis, a multivariable analysis was conducted to estimate the effect of the 2D and 3D LAVI and the presence or absence of carotid plaques (CP) on the DSE result after adjusting for other demographic, clinical, and echocardiographic variables. Receiver operating characteristic (ROC) curves were finally plotted in order to find the optimal cut-off value (highest sensitivity and specificity) of the 2D and 3D derived LAVI that best discriminated patients with a positive or a negative DSE result. P-values (2-sided) <0.05 were considered significant. All statistical calculations were performed with the use of the SPSS 16 package for Windows.

**Results**

The indications for DSE are depicted in Table 1. The main indication was chest pain (68% of patients) and 42% of these patients had a known history of CAD, documented by either previous angiography or a history of myocardial infarction. The patients’ baseline characteristics are shown in Table 2.

DSE was abnormal in 50 (38.5%) out of 130 patients studied. Patients with an abnormal DSE result were older (66.3 ± 12.4 vs. 60.8 ± 10.4 years, P = 0.010) and more often reported a history of hypertension (79.6 vs. 41.0%, P = 0.032) and/or previous myocardial infarction (40.0 vs. 16.2%, P = 0.004). All other baseline clinical characteristics were similar between the two groups (Table 2). In addition, patients with a positive DSE more frequently demonstrated chest pain during the test (52.0 vs. 26.2%, P = 0.005).

When comparing the echocardiographic characteristics of the two groups, we found that patients with an abnormal test result had higher values of the 3D maximum LAVI (31.5 ± 8.2 vs. 27.4 ± 7.4 mL/m², P = 0.004). On the other hand, the two groups did not differ significantly on the 2D derived maximum LAVI measurements (36.2 ± 9.5 vs. 34.2 ± 11.2, P = 0.299).
the presence of plaques in the carotid arteries (89.1 vs. 76.2%, \( P = 0.100 \)).

Two-dimensional maximum LAVI measurements correlated modestly with 3D maximum LAVI values \((r = 0.681, P < 0.0001)\), although the former were higher (Bland–Altman bias: 6.05 ± 7.77 mL/m²; Figures 3 and 4).

A multivariable logistic regression analysis was conducted to estimate the relative importance of each of the variables that were found to be significant in univariate analysis in predicting an abnormal DSE result (Table 3). Chest pain during DSE and a history of a previous myocardial infarction were found to be the most important predictors of a positive test. In addition, age and the 3D maximum LAVI were also able to predict the result of DSE in our population, where hypertension was not.

ROC curves were created for both 2D and 3D maximum LA volume-derived parameters, in an attempt to define cut-off values that could discriminate patients with abnormal DSE from normals (Figure 5). The 3D, but not 2D, maximum LAVI was better than chance for predicting the DSE result (area under curve = 0.651, \( P = 0.004 \) for 3D; and area under curve = 0.571, \( P = 0.171 \) for 2D echocardiography). There was no specific cut-off 3D maximum LAVI value with a high predictive ability to discriminate between true positive from false positive DSE results. However, a cut-off value for 3D maximum LAVI of 24.5 mL/m² had a sensitivity of 80% and a negative predictive value of 77% for an abnormal test result, whereas a cut-off value of 36 mL/m² had a specificity of 93% and a positive predictive value of 72% for an abnormal DSE (Table 4).

Intraobserver \((r = 0.997, P < 0.0001, \text{Bland–Altman bias} = 1.61 ± 1.06 \text{mL})\) and inter-observer \((r = 0.961, P < 0.0001, \text{Bland–Altman bias} = -0.33 ± 4.04 \text{mL})\) variability for 3D LAVI measurements was found to be excellent. The analysis time was significantly shorter for 2D compared with 3D LA volume analysis \((1.0 ± 0.5 \text{ vs } 6.0 ± 2.0 \text{ min}, P = 0.0001)\).

**Discussion**

In this study, we used two relatively simple parameters: 3D maximum LAVI and CP, in an attempt to determine their potential value in predicting the result of DSE in patients with normal wall motion at rest. The rationale for using the LAVI is based on increasing evidence that the LA size is an important source of diagnostic and prognostic information in patients with left ventricular systolic and diastolic dysfunction because it reflects the magnitude and duration of elevated left ventricular filling pressures and, thus, is a marker of the severity and chronicity of...
It is also well established that in patients with ischaemic heart disease subclinical diastolic dysfunction precedes systolic abnormalities.24,25 It was only recently that the role of the LA size, traditionally assessed by M-mode or 2D methods, was found to be useful in predicting the result of stress (exercise or dobutamine) echo and also enhance prognostic information.5,6 Unlike 2D echocardiography, 3D echocardiography does not require geometric assumptions and is even more accurate when compared with the gold standard technique of magnetic resonance imaging (MRI).26–28,31 Although, 2D LA volume assessment with the biplane method has also been shown to correlate well with 3D calculations31–34 and with MRI,31 the reported correlation was not as good as the one between 3D and MRI.

An important finding in the present study is that the intra- and inter-observer variability for 20 randomly selected 3D LAVI measurements was excellent. This is consistent with the findings of other studies31–34 and demonstrates that 3D LAVI assessment is a reproducible measurement for estimation of the LA volume. No intra- and inter-observer variability testing for 2D biplane area—length was made since it has proved to be very good in previous studies.32 A limitation of 3D LAVI calculations is that it is significantly more time consuming than 2D measurements as demonstrated in the present study, as well as in previous studies,32,33,35 although not all authors agree on this.31 Moreover, access to sophisticated 3D software is required, which may not be available in all echocardiographic departments.

Table 1  Indications of dobutamine stress echocardiography in our study population

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No known CAD: chest pain</td>
<td>51 (39.3%)</td>
</tr>
<tr>
<td>No known CAD: exertional dyspnoea</td>
<td>15 (11.5%)</td>
</tr>
<tr>
<td>Known CAD: chest pain</td>
<td>37 (28.5%)</td>
</tr>
<tr>
<td>Known CAD: exertional dyspnoea</td>
<td>12 (9.2%)</td>
</tr>
<tr>
<td>Preoperative evaluation</td>
<td>3 (2.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (9.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>130 (100%)</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease.
To our knowledge, the only study up to date evaluating the role of the LA size in predicting the result of stress echocardiography is that of Alsaileek et al. They studied 180 randomly selected patients who underwent exercise or DSE for known or suspected CAD and found that a normal resting maximum LAVI (≤28 mL/m²) as assessed retrospectively by the biplane area—length method had a negative predictive value of 94% for an abnormal DSE, although the sensitivity and positive predictive value of this cut-off point were low. In addition, the larger the LAVI, the more likely the presence of abnormal wall motion on stress echocardiography. In our study, patients with abnormal DSE did not differ significantly from normals as far as 2D maximum LAVI measurements were concerned. Many reasons may have accounted for this difference. First of all we excluded patients with WMAs at rest, whereas Alsaileek et al. did not (over 25%...
of their whole population had WMAs at baseline). In addition, the proportion of positive DSE test results was higher in our study (38.5% vs. 31.7%). This could be due to the much higher number of patients (43 vs. 17%, respectively) who had a known history of CAD in our study, as well as different ways of interpretation of DSE. Since in the study of Alsaileek et al., no 3D LAVI measurements were made, it is unknown if this could change the interpretation of the results. Irrespective of all the above, it is worth noting that in both studies no cut-off value was found to have exceptionally good sensitivity and specificity in predicting the result of DSE. In contrast to 2D, no widely accepted normal values for 3D maximum derived volumes have been determined so far. On the basis of our results, we propose two cut-off values for the 3D maximum LAVI that could be useful in DSE interpretation. Specifically, patients with 3D LAVI \( \leq 24.5 \text{ mL/m}^2 \) are unlikely to have a positive DSE (80% sensitivity and 77% negative predictive value), whereas patients with 3D LAVI \( > 36 \text{ mL/m}^2 \) are unlikely to have a negative stress test result (93% specificity and 72% positive predictive value). The clinical significance of 3D LAVI measurements between 24.5 and 36 \text{ mL/m}^2 in predicting the DSE result is less clear; in general the higher the 3D maximum LAVI, the higher is the probability of a positive DSE, as demonstrated in our multivariable analysis. Obviously, better standardization of the method and application of these cut-off values in larger populations will be useful in determining their real importance in everyday clinical practice.

As far as CP are concerned, limited data exist on the incremental value of estimating carotid artery morphology in patients undergoing stress testing. Kanwar et al. tested this hypothesis in a population of 50 symptomatic patients without a known history of CAD who underwent exercise (or pharmacologic) stress testing, and demonstrated that, in a small subset of patients with an equivocal (i.e. non-diagnostic, suboptimal, possibly artefactual, or minimally abnormal) stress test result, a negative carotid plaque finding had a negative predictive value of 100% for the presence of CAD, as assessed subsequently by coronary angiography. In our study, patients with an abnormal test did not demonstrate a higher frequency of CP compared with normals, and thus carotid scanning proved to be of little use in predicting the result of DSE. This may be explained by the fact that although the presence of CP may indicate the presence of plaques in the coronary tree, it does not necessarily mean that these plaques cause flow-limiting stenoses, which must be present in order to be detected by DSE. In addition, significant methodological differences (exclusion of patients with-equivocal tests in our project and almost exclusive use of other stress modalities than DSE in their study) exist between the two studies and may account for the different results. Interestingly however, in both studies a similar proportion of patients had plaques in their carotids (78 vs. 76%).

**Limitations**

First of all, the relatively small study population \((n = 130)\) of which 38.5% had a positive DSE result may have influenced the results. Furthermore, no correlation with angiographic results was made. However, we deliberately avoided including angiographic results because of the risk of a referral bias (only patients with positive DSE are usually referred for an angiogram), as well as the inability of routinely conducted invasive procedures to detect causes of ischaemia other than epicardial coronary disease. Furthermore, although the DSEs were interpreted by an experienced observer,
this is, as discussed, a subjective evaluation and a different observer may have led to different results. In addition, although 3D LA volume analysis makes it possible to calculate additional parameters of LA function, such as the minimum LA volume, LA total stroke volume, and LA total ejection fraction, we avoided using these parameters because solid data of their usefulness are lacking in the literature for both 2D and 3D echocardiography in CAD patients. Similarly, we avoided estimating LA volumes during stress for two reasons: first, it would be even more time consuming to analyze multiple 3D data sets (our aim was to find simple parameters to aid in DSE interpretation); and secondly, the use of continuous infusion of contrast in the majority of our patients would make 3D LA volume acquisition not feasible (with the echo machines used at the time of the study), due to low volume rates at higher heart rates. However, we do recognize that LA volumes change during stress, and serial measurements might be useful in delineating the sequence of events following myocardial ischemia. Finally, better standardization of the 3D maximum LAVI calculation would be useful, in order for potentially useful 3D derived measurements to be more easily adopted in everyday clinical practice.

Conclusions
Three-dimensional (but not 2D) maximum LAVI measurements are increased in patients with abnormal DSE compared with those with a normal test. The 3D LAVI as a continuous variable is able to predict the result of DSE. A 3D maximum LAVI ≤ 24.5 mL/m² is able to predict a normal DSE, whereas a 3D LAVI measurement >36.0 mL/m² can predict an abnormal DSE. Carotid scanning did not prove to be useful in predicting the result of DSE in the present study. The above findings may be useful in indeterminate DSE cases to help decide if the test is normal or not. Importantly, 3D LAVI measurements can be incorporated into a clinical DSE relatively easily, with minimal disruption to the patient’s workflow.

Conflict of interest: none declared.

References


