Initial experience using contrast enhanced real-time three-dimensional exercise stress echocardiography in a low-risk population

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Abstract

Although emerging data support the utility of real-time three-dimensional echocardiography (RT3DE) during dobutamine stress testing, the feasibility of performing contrast enhanced RT3DE during exercise treadmill stress has not been explored. Two-dimensional (2D) and three-dimensional (3D) acquisition were performed in 39 patients at rest and peak exercise. Contrast was used in 29 patients (74%). Reconstruction was performed manually by generating short axis cut planes at the base, mid-ventricle and apex, and automatically by generating 9 short axis slices. Three-dimensional acquisition was feasible during rest and stress regardless of the use of contrast. Time to acquire stress images was reduced using 3D (35.2±17.9 s) as compared to 2D acquisition (51.6±14.7 s; P<0.05). Using a 17-segment model, of all 663 segments, 588 resting (88.6%) and 563 stress segments (84.9%) were adequately visualized using manually reconstructed 3D data, compared with 618 resting (93.2%) and 606 stress segments (91.4%) using 2D data (P rest=0.06; P stress=0.07). We concluded that contrast enhanced RT3DE is feasible during treadmill stress echocardiography.

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Introduction

Treadmill stress echocardiography is a validated clinical procedure used routinely to diagnose the presence and extent of coronary artery disease as well as predict prognosis of certain patients.[1] The diagnostic accuracy of conventional two-dimensional stress echocardiography (2DSE) is limited by technical considerations and is therefore highly dependent on the sonographer's scanning skills. Stress images should be acquired as close as possible to peak exercise, preferably within a narrow window of 60-90 seconds, while coordinating patient and respiratory movement.[2] Since the rest and stress images are compared side by side, it is critical to obtain identical views by duplicating the exact transducer position for rest and stress, which can be challenging, especially if the scanning position the patient assumes post stress is slightly different than the resting scanning position. Therefore, the sensitivity and specificity of 2DSE are frequently limited by the impact of these technical issues on image acquisition and quality.

Advances in transducer and computing technology have fostered the development of real-time three-dimensional echocardiography (RT3DE).[3-6] RT3DE allows for acquisition of the entire left ventricle (LV) over 4 cardiac cycles from a single transducer position. The full volume data of the left ventricle can be sectioned in a proper format, eliminating the common problem of foreshortening of the LV apex. Moreover, the LV during rest and stress can be aligned anatomically and spatially to achieve the most accurate comparison of pre-stress and post-stress imaging.[7]

While the feasibility of using older generation RT3DE during exercise stress testing has been demonstrated,[8,9] most of the current literature supporting the use of second generation live RT3DE is available for bicycle exercise and dobutamine stress,[10-16] with only 2 studies describing the use of the newer technology during treadmill stress echo.[17,18] Importantly, the use of contrast to enhance endocardial border definition during stress testing is currently widely used and well supported in the literature; however the feasibility of contrast enhanced treadmill stress echo using live RT3DE has not been demonstrated.

The purpose of this study is to evaluate the feasibility of second generation live RT3DE echocardiographic imaging during treadmill exercise stress echocardiography in non-selected patients who present for a clinically indicated stress echocardiogram and who, therefore, may require the use of contrast. In addition, two different cropping techniques will be used for off line cropping and reconstruction and the data generated compared.

Materials and Methods

Patient population

The study population includes patients over 18 years of age, in sinus rhythm and capable of exercising to target heart rate on a treadmill, who were referred for a clinical treadmill stress echocardiogram. The indication in all patients was to exclude the presence of coronary artery disease. Patients were prospectively enrolled in the study after informed consent was obtained. The institutional review board of Stony Brook University Medical Center approved the study.

Two-dimensional exercise stress echocardiography

After electrocardiographic leads were placed, pre-exercise images were obtained in a left lateral decubitus position. All patients then exercised using a standard Bruce protocol. End points for test termination were followed according to standard clinical procedures for exercise stress testing.[19] Two-dimensional post-exercise images were acquired within 90 seconds of stopping the treadmill in the same position used for resting imaging. Both rest and stress 2D echocardiographic images were obtained using a commercially available ultrasound machine (iE33, Philips, Andover, MA, USA) using a broadband S5 transducer (1-5 MHz). A quadscreen display was used to display the following imaging planes: parasternal long axis, parasternal short axis at the level of the papillary muscles, parasternal short axis at the level of the apex, apical 4, 2 and 3 chamber. A standard side-by-side comparison of rest and peak stress images for wall motion analysis was performed. When contrast was required, loops were recorded after injection of contrast agents at baseline and peak stress. Use of echocardiographic contrast was at the discretion of the sonographer based on the quality of the 2D images, according to standard recommendations.[20,21] The echocardiographic contrast agent used for endocardial border enhancement was Definity (Bristol-Myers Squibb, N. Billerica, MA, USA). The contrast agent was administered in the form of a bolus through a peripheral IV line (0.1 mL of 1:12 mL normal saline dilution).

Real-time 3D echocardiography acquisition protocol

Real-time 3D imaging was performed with a matrix array transducer to obtain a pyramidal full volume data set from both apical and parasternal windows (Philips iE33, X3-1 x Matrix, 3-1 MHz; Phillips, Andover, MA, USA). Real-time 3D images were obtained immediately after 2D images during both rest and stress. Care was taken to include the entire LV cavity within the pyramidal volume scan. A wide-angled acquisition mode was used (93×80 degrees) in which 4 wedge-shaped sub-volumes (93×20 degrees each) were obtained over 4 consecutive cardiac cycles, during a single breath hold at end-expiration. Acquisition was performed, as triggered by the R wave of the electrocardiogram, for a total of 4 heartbeats. Real-time 3D data sets were then transferred and stored on a dedicated workstation to be further reconstructed and analyzed off line using commercial software (QLAB, Versions 4.0, Philips, Andover, MA). The time to acquire 3D stress images was measured and compared to the time to acquire 2D stress images. Whenever contrast was used to enhance the 2D images acquired, it was also given during the 3D image acquisition, using the same contrast administration protocol. The frame rates of the real time 3D echocardiography ranged from 16 to 20 frames per second depending on the depth of the imaging plane.

Image review and analysis

A 17 segment model was used for wall motion analysis on the 2D images as recommended by the American Society of Echocardiography.[22] Wall motion score index was calculated by 2 expert echocardiographers who were blinded to the clinical data of the patients as well as to results of the 3DSE. Wall motion in each of the 17 segments was scored as: 1 = normal, 2 = hypokinesis, 3 = akinesis, and 4 = dyskinesis. The total score was then divided by the number of segments seen to calculate the score index. Three-dimensional reconstructions were performed manually by generating short axis cut planes at the base, mid-ventricle and apex for both rest and stress (QLAB analysis) and automatically by generating 9 short axis slices through the left ventricle (iSlice, 3DQ Advanced analysis). Two echocardiographers reviewed the images independently and were blinded to the clinical data and the 2D data analysis. The number of visualized segments at baseline and following stress, wall motion score, wall motion score index, time to perform manual reconstructions and time to perform iSlice analysis were compared. A stress echocardiogram was considered positive for ischemia when a stress-induced wall motion abnormality was noted in one or more segments or when the wall motion score was greater than 1. Wall motion segments that remained hypokinetic or akinetic at peak stress, unchanged compared with rest images, were considered infarcted segments. A stress echocardiogram was classified as positive for coronary artery disease if there was evidence of ischemia or infarction. The same criteria were used for both 2D and 3D images.

Statistical analysis

Continuous variables were expressed as the mean value ± SD. Data obtained with 2D and 3D techniques were compared using unpaired t-tests. Simple linear regression analysis was performed to determine correlation between wall motion score index (WMSI) by 2D and manual 3D, and between 2D and automated 3D (iSlice), as well as between manual and automated 3D. A probability level of less than 0.05 was considered statistically significant.

Results

Thirty-nine patients with a mean age of 51.2±12.3 years were enrolled. All patients completed the exercise treadmill portion of the stress test and reached target heart rate (85% of maximum predicted heart rate). Contrast was administered to 74% of subjects during 2D and 3D imaging without any adverse reactions. The baseline patients' characteristics are shown in Table 1. A history of chest pain was present in 83% of patients whereas 5% of patients had a prior history of coronary artery disease, myocardial infarction or revascularization. Moreover, 8% had peripheral arterial disease, 38% had hypertension, 56% had hypercholesteremia, 15% had type 2 diabetes, and 33% were active smokers.

Hemodynamic characteristics of study population

The baseline and exercise hemodynamics are presented in Table 2. Heart rate increased from an average of 65±10 to an average of 166±20 bpm ($P<0.05$). Systolic blood pressure increased from 125±20 to 163±24 mm Hg ($P<0.05$). The most common reasons for termination of the test were fatigue (56%) and shortness of breath (33%). There were no significant arrhythmias or significant ischemic changes on the ECG necessitating premature termination of the stress protocol in any of the patients.

Feasibility of acquiring and interpreting real-time 3D images during exercise stress echocardiography

Three-dimensional acquisition of a full volume data set was feasible in all patients during rest and stress regardless of the use of contrast. Time to acquire stress images was significantly shorter using 3D (35.2±17.9 s) than 2D (51.6±14.7 s; $P<0.05$). The full volume data set acquired was reconstructed using both manual and automated reconstruction techniques. A representative example of manual reconstruction is shown in Figure 1 (panels A-B), and of automated reconstruction in Figure 2 (panels A-B). Of the potential 663 segments reconstructed using the 17-segment model, 588 resting segments (88.6%) and 563 stress segments (84.9%) were adequately visualized using manually reconstructed 3D data. The number of segments visualized using 2D data was slightly higher but not significantly so: 618 resting segments (93.2%) and 606 stress segments (91.4%) were visualized using 2D data (P rest=0.06; P stress=0.07; Table 3). When comparing individual segments we found that the basal anterior and basal anterolateral segments acquired following stress were the least likely to be visualized using either manual or automated 3D reconstruction. An example of an abnormal 3D exercise stress echocardiogram is demonstrated in Figure 3.

Comparison between 2D and 3D exercise stress echocardiography interpretation

The wall motion score index of the visualized segments acquired by 2D was 1.00±0.04 at

Table 1. Clinical characteristics of the 39 study patients.

Variable	Value (%)
Age, mean yrs (SD)	51.9±12.3
Men # (%)	17 (43)
Clinical diagnosis	
Chest pain	32 (83)
Known CAD	2 (5)
Previous PCI	2 (5)
Previous CABG	0 (0)
Previous MI	2 (5)
Coronary risk factors	
Hypertension	15 (38)
Hypercholesterolemia	22 (56)
Diabetes	6 (15)
Family history	11 (28)
Peripheral vascular disease	3 (8)
Tobacco abuse	13 (33)
Medications	
Beta-blockers	5 (13)
Nitrates	1 (3)
Calcium channel blocker	2 (5)
ACE inhibitor	5 (13)
Angiotensin receptor blocker	4 (10)
Aspirin	6 (15)
Statin	13 (33)

CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; tobacco, designates active tobacco use; ACE, angiotensin converting enzyme.

Table 2. Exercise stress echocardiography data of the 39 patients.

Variable	R
Total exercise time (min)	9.6±2.5
Endpoint, n (%)	
Achievement of target heart rate	1 (2)
Completion of stress protocol	0 (0)
Fatigue	22 (56)
Claudication	2 (5)
Chest pain	1 (3)
Shortness of breath	13 (33)
Significant ST depression	0 (0)
Significant arrhythmia	0 (0)
Severe hypertension	1 (3)
Other	4 (10)
Baseline hemodynamic data	
Heart rate (bpm)	65±10
Systolic blood pressure (mm Hg)	125±20
Diastolic blood pressure (mm Hg)	75±7
Peak stress hemodynamic data	
Heart rate (bpm)	166±20 *
Systolic blood pressure (mm Hg)	163±24 *
Diastolic blood pressure (mm Hg)	77±9
Rate-pressure product	26963±5445

Values are ± SD. * P < 0.05 when compared to resting values.

Table 3. Manually reconstructed 3D data versus standard 2D data.

Segments visualized	Number	P
# segments (%), Rest 3D	588	0.06
# segments (%), Rest 2D	618	
# segments (%), Stress 3D	563	0.07
# segments (%), Stress 2D	606	
Total potential number of segments: 663		

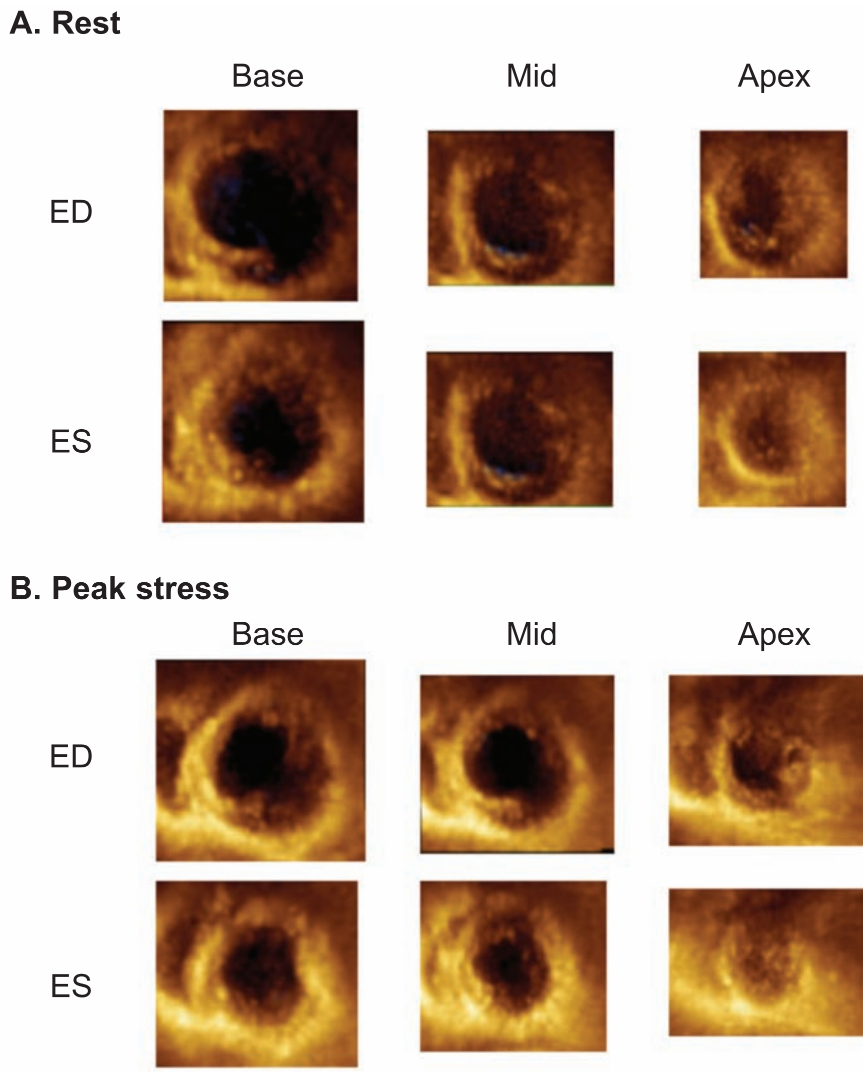


Figure 1. Three-dimensional demonstration of normal wall motion response in a single patient to exercise stress using manual reconstruction. (A) Baseline non-contrast cropped short axis images from base (left) to apex (right), at end diastole (ED, top) and end systole (ES, bottom). (B) Cropped short axis images at peak exercise stress in equivalent slices. Note smaller left ventricular cavity size.

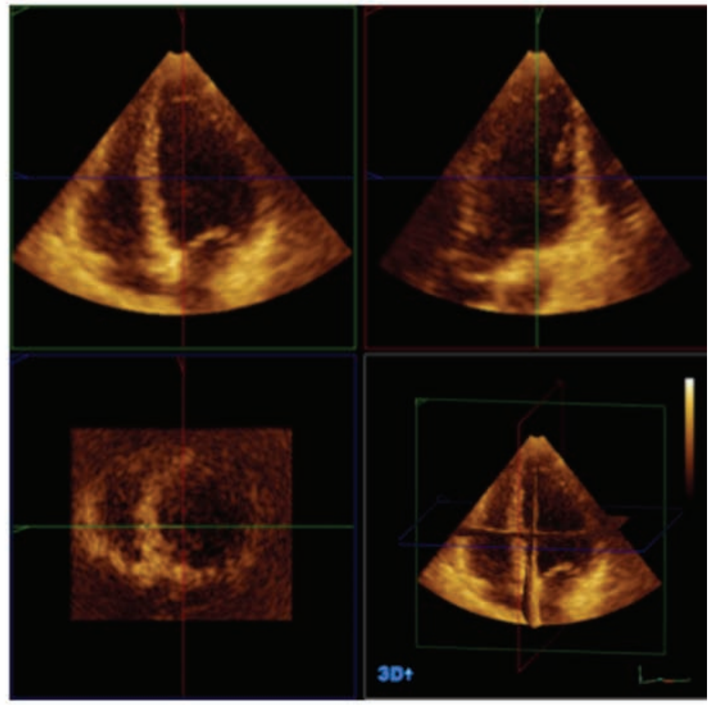
rest and 1.02±0.07 at peak exercise. The wall motion score index of the visualized segments acquired by 3D was 1.01±0.04 at rest and 1.02±0.05 at peak stress when data reconstructed manually, and 1.00±0.03 at rest and 0.98±0.17 at peak stress, when reconstructed automatically. There was no significant difference in wall motion score index (WMSI) calculated from the 2D data compared with the 3D data analyzed by either manual technique (P=0.45 at rest and 0.60 at stress) or the automated technique ((P=0.34 at rest and 0.09 at stress). At rest, good correlation exists between 2D and 3D manual reconstruction (r=0.67), as well as between 2D and 3D automated reconstruction (r=0.63) for WMSI. However, at peak stress, poor correlation exists between 2D and 3D manual reconstruction (r=0.24), and between 2D and 3D automated reconstruction (r=0.18). When analyzing the data by patients not by individual segments, rest 2D acquisition revealed wall motion abnormalities in 2 patients and normal wall motion in 37 patients, whereas manually reconstructed rest 3D data demonstrated abnormal and normal wall motion in 6 and 33 patients, respectively. When the same 3D data was reconstructed automatically, abnormal wall motion was seen in 5 patients, 33 patients had no wall motion abnormalities, and it was not possible to interpret findings in one patient due to image quality. During peak exercise, 2D acquisition demonstrated wall motion abnormalities in 5 patients and normal wall motion in 34 patients, whereas manual reconstructions of the 3D data depicted abnormal wall motion in only 4 patients and normal wall motion in 35 patients. Automated reconstructions of the same 3D data depicted wall motion abnormalities in only 2 patients, with 36 patients interpreted as having no wall motion abnormalities, and it was not possible to interpret findings in one patient due to image quality. The heart rate was significantly slower at the time of 3D image acquisition compared with 2D acquisition (107±19.4 bpm vs. 166±19.8 bpm respectively; P<0.05) during peak stress in the patients with discrepancy between 2D and 3D stress interpretation.

Comparison between automated reconstruction and manual reconstruction of the full volume 3D datasets

Significantly more segments were seen using manual reconstruction than automated reconstruction (iSlice) for both rest 3D (588 vs. 491; P<0.05) and stress 3D data (563 vs. 483; P=0.03; Table 3). When calculating wall motion score index we found no significant difference between the two techniques when used to reconstruct 3D data at rest (P=0.10) and at peak exercise (P=0.13).

Manual reconstruction of 3D data acquired during both rest and stress required more time than automated reconstruction. Although the difference in time between the two reconstruction techniques was not significant (86±61 vs. 102.4±44 s; P=0.19) when used to analyze data acquired at peak stress, manual reconstruction of resting data required significantly more time to process than automated reconstruction (112.1±55 s vs. 87.4±40 s; P=0.02).

A. Rest



B. Rest

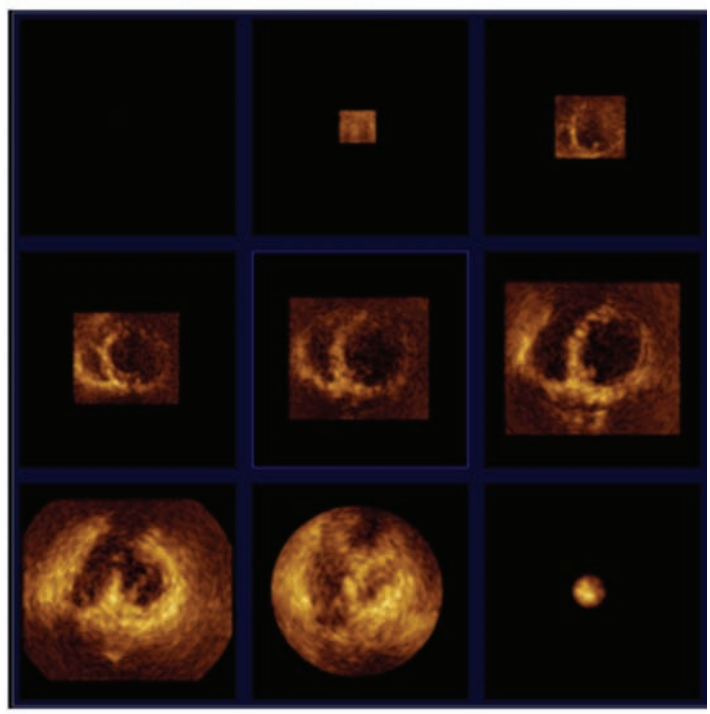


Figure 2. Three-dimensional representation using iSlice software for the same patient as in Figure 1. (A) Rest images, with cropped planes automatically cut. (B) Rest images, automatically cropped.

Discussion

The role of real-time three-dimensional echocardiography for assessment of left ventricular volume and systolic function during rest is well documented. Although some data are available supporting the use of RT3DE during dobutamine stress echo,[10,13,14] there is less information to support the routine use of second generation live RT3DE during exercise treadmill stress.[17,18] Echocardiographic imaging during or immediately post exercise stress is notoriously more challenging than during dobutamine stress. Therefore, the implementation of 3D imaging at rest and peak stress is an attractive option, as it allows for visualization of the entire LV in multiple planes by cropping the volumetric data set within a short period of imaging time post exercise.

The use of contrast during stress echocardiography has been shown to improve the overall diagnostic power of the study by reducing interobserver variability,[23] increasing the diagnostic accuracy[23] and improving the cost benefit ratio in diagnosing ischemia in patients with coronary artery disease.[24] It is, therefore, likely that contrast may improve the diagnostic power of RT3D stress echocardiography; however, at present there are no data to support this combination. It has been demonstrated that contrast can be used during resting RT3DE acquisition and was shown to improve image quality.[25] Furthermore, LV volumes generated by 3D echo while using contrast correlate well with anatomic volumes in an animal model.[26] Our study has demonstrated for the first time the feasibility of combining 3D stress echocardiography with the use of contrast. Furthermore, we have shown that regardless of the use of contrast, image acquisition using RT3DE is faster compared with

2D with a 16 second average difference between the two techniques. This finding is similar to previously published data in this regard,[9] where an approximately 10 second advantage was observed for 3D acquisition over 2D. This shorter acquisition time could potentially be advantageous when scanning patients with mild CAD and transient wall motion abnormalities that could normalize before image acquisition is completed. It is important to note that interpretation of 3D data requires off line reconstructions which is time consuming, although it does not require the patient to be present. Our study demonstrates similar interpretation of the 2D and 3D images acquired at both rest and stress. We found no significant differences between wall motion score index calculated from the 2D data compared with the 3D data analyzed by either one of the 3D reconstruction techniques used. Likewise, there was also good correlation between 2D and 3D for calculation of wall motion score index at rest. However, at peak stress, correlation was poor despite a larger and similar number of segments visualized by both modalities. The most likely explanation for this discrepancy is the difference in heart rate at the time of acquisition of peak stress 2D data and peak stress 3D data. The 3D data was acquired after the 2D, which could have given time for wall motion abnormalities to resolve. Although 3D imaging technology is currently limited by lower frame rates during fast HR, high concordance between 3D dobutamine stress echocardiography and 2D was demonstrated[10] when both were acquired at similar heart rates.

When considering patients, not individual segments, 3D analysis using manual reconstructions at rest identified 4 additional patients as having wall motion abnormalities. Since there was no correlation by cardiac catheterization or by myocardial single photon emission computed tomography (SPECT), it is unclear whether this is related to higher sensitivity or lower specificity of 3D over 2D. During exercise, manual reconstructions of the 3D data failed to recognize wall motion abnormalities in one patient diagnosed with wall motion abnormalities by 2D. This could be explained by lower sensitivity of 3D over 2D during the more challenging scanning phase, or more likely, could be explained by lower heart rate at the time of 3D acquisitions, as explained above. When applying both reconstruction methods to the same 3D data, we found that the automated method failed to diagnose 2 additional patients with wall motion abnormalities while one patient could not be interpreted. The difference between the two reconstructions methods could be partially explained by poorer image quality observed with the automated reconstruction methods. In addition, the ability to generate the short axis cut planes manually may allow for better alignment of the images in relation to fixed cardiac structures (such as the papillary muscles). Automated software may fail to account for changes in the cardiac orientation at peak stress, which may be different than the resting orientation.

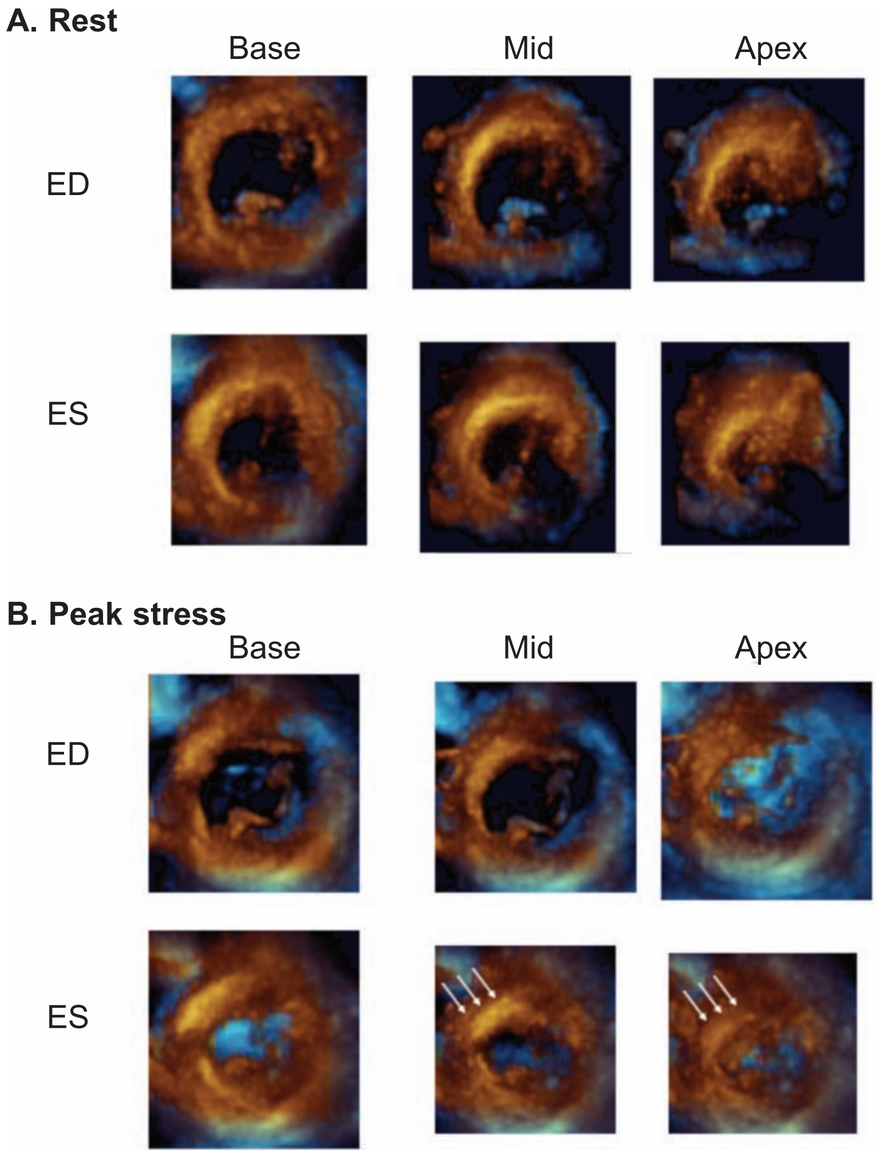


Figure 3. Three-dimensional representation of ischemia in the anteroseptal distribution using manual reconstruction. (A) Baseline cropped short axis images from base (left) to apex (right), at end diastole (ED) and end systole (ES). (B) Cropped short axis images at peak exercise stress in equivalent slices. Note left ventricular cavity as ES was larger at peak stress. In addition, there is lack of thickening in the anteroseptal distribution (arrowheads), suggestive of ischemia.

Study limitations

The main objective of our study was to assess the feasibility of using RT3DE in combination with contrast injection during treadmill stress. The sensitivity and specificity of RT3DE for detection of CAD cannot be determined from our study since a gold standard evaluation with cardiac catheterization was not performed on our patients. Moreover, the majority of the patients had a normal stress echocardiogram, which may be related to the relatively small number of patients in the study or an institutional referral bias in which low-risk patients may be preferentially referred for exercise stress echocardiography. The greatest limitation in comparing the 2D and 3D data is the difference in heart rate between 2D and 3D acquisition. However, the goals of this study were to assess the feasibility of acquiring 3D data at peak exercise stress regardless of the use of contrast, and to compare 2 available reconstruction methods for their ability to generate resting and stress myocardial segments.

We believe that these goals were met regardless of the limitations listed above.

Future directions

We demonstrate the feasibility of acquiring 3D data during stress. A next step could be to use this technology to prospectively study a more heterogeneous patient population that includes more patients with significant coronary artery disease as performed by Peteiro *et al.*[18] Ideally, the patient population would undergo coronary angiography and this information could be used to determine sensitivity and specificity of 3D in diagnosis of coronary artery disease. The shorter acquisition time provided by 3D compared with 2D has a great potential in further improving the diagnostic accuracy of stress echocardiography but also requires further exploration. Current and future improvements in technology such as one beat acquisition and a transducer with a smaller footprint, as well as development of improved automated reconstruction software will further accelerate wide dissemination of this technology in clinical practice. Future investigations could explore the potential added value of contrast in 3D treadmill stress echocardiography in patients with CAD.

Conclusions

We demonstrate the feasibility of performing live real-time 3D echocardiographic acquisition during treadmill stress echocardiography even when contrast is used. The 3D acquisition time is significantly shorter than 2D image acquisition, therefore shortening the delay from peak stress to data acquisition, potentially allowing greater opportunity for the detection of transient wall motion abnormalities. We found that this shorter acquisition time did not compromise the ability to analyze the data, and demonstrated a similar number of segments visualized using both imaging modalities.

Whereas manual reconstruction of the full volume data set is slightly more time consuming than automated reconstruction, it allows visualization of significantly more myocardial segments. The number of segments visualized and wall motion analysis is comparable to that obtained by 2D when the 3D images are acquired at a slower heart rate, and may prove to be a more sensitive tool; however, future studies with more patients and comparison with anatomical data are required in order to address its sensitivity and specificity for the detection of coronary artery disease.

References

1. Pellikka PA, Nagueh SF, Elhendy AA, et al. American society of echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 2007;20:1021-41.
2. Armstrong WF, Zoghbi WA. Stress echocardiography: current methodology and clinical applications. J Am Coll Cardiol 2005; 45:1739-47.
3. Collins M, Hsieh A, Ohazama CJ, et al. Assessment of regional wall motion abnormalities with real-time three-dimensional echocardiography. J Am Soc Echocardiogr 1999;12:7-14.
4. Sugeng L, Weinert L, Lang R. Left ventricular assessment using real-time three dimensional echocardiography. Heart 2003;89:29-36.
5. Hung J, Lang R, Flachskampf F, et al. 3D echocardiography: A review of current status and future directions. J Am Soc Echocardiogr 2007;20:213-33.
6. Nanda NC, Miller AP. Real time three-dimensional echocardiography: Specific indications and incremental value over traditional echocardiography. J Cardiol 2006;48:291-303.
7. Shekhar R, Zagrodsky V, Garcia M, Thomas JD. Registration of real-time 3-D ultrasound images of the heart for novel 3-D stress echocardiography. IEEE Trans Med Imaging 2004;23:1141-9.
8. Zwas DR, Takuma S, Mullis-Jansson S, et al. Feasibility of real-time 3-dimensional treadmill stress echocardiography. J Am Soc Echocardiogr 1999;12:285-9.
9. Sugeng L, Kirkpatrick J, Lang R, et al. Biplane stress echocardiography using a prototype matrix-array transducer. J Am Soc Echocardiogr 2003;16:937-41.
10. Takeuchi M, Otani S, Weinert L, et al. Comparison of contrast-enhanced real-time live 3-dimensional dobutamine stress echocardiography with contrast 2-dimensional echocardiography for detecting stress-induced wall-motion abnormalities. J Am Soc Echocardiogr 2006;19:294-9.
11. Matsumura Y, Hozumi T, Arai K, et al. Non-invasive assessment of myocardial ischaemia using new real-time three-dimensional dobutamine stress echocardiography: comparison with conventional two-dimensional methods. Eur Heart J 2005;26:1625-32.
12. Yang HS, Pellikka PA, McCully RB, et al. Role of biplane and biplane echocardiographically guided 3-dimensional echocardiography during dobutamine stress echocardiography. J Am Soc Echocardiogr 2006;19:1136-43.
13. Aggeli C, Giannopoulos G, Misovoulos P, et al. Real-time three-dimensional dobutamine stress echocardiography for coronary artery disease diagnosis: Validation with coronary angiography. Heart 2007; 93:672-5.
14. Pulerwitz T, Hirata K, Abe Y, et al. Feasibility of using a real-time 3-dimensional technique for contrast dobutamine stress echocardiography. J Am Soc Echocardiogr 2006;19:540-5.
15. Ahmad M, Xie T, McCulloch M, et al. Real-time three-dimensional dobutamine stress echocardiography in assessment of ischemia: Comparison with two-dimensional dobutamine stress echocardiography. J Am Coll Cardiol 2001;37:1303-9.
16. Walimbe V, Garcia M, Lalude O, et al. Quantitative real-time 3-dimensional stress echocardiography: a preliminary investigation of feasibility and effectiveness. J Am Soc Echocardiogr 2007;20:13-22.
17. Jenkins C, Haluska B, Marwick TH. Assessment of temporal heterogeneity and regional motion to identify wall motion abnormalities using treadmill exercise stress three-dimensional echocardiography. J Am Soc Echocardiogr 2009;22:268-75.
18. Peteiro J, Piñon P, Perez R, et al. Comparison of 2- and 3-dimensional exercise echocardiography for the detection of coronary artery disease. J Am Soc Echocardiogr 2007;20:959-67.
19. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 2002;40: 1531-40.
20. Mulvagh SL, Rakowski H, Vannan MA, et al. American Society of Echocardiography consensus statement on the clinical applications of ultrasonic contrast agents in echocardiography. J Am Soc Echocardiogr 2008;21:1179-201.
21. Wagoner AD, Ehler D, Adams D, et al. Guidelines for the cardiac sonographer in the performance of contrast echocardiography: recommendation of the American society of echocardiography council on cardiac sonography. J Am Soc Echocardiogr 2001;14:417-20.
22. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in

conjunction with the European association of echocardiography, a branch of the European society of cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
23. Dolan MS, Riad K, El-Shafei A, et al. Effect of intravenous contrast for left ventricular opacification and border definition on sensitivity and specificity of dobutamine stress echocardiography compared with coronary angiography in technically difficult patients. Am Heart J 2001;142:908-15.
24. Thanigaraj S, Nease RF Jr, Schechtman KB, et al. Use of contrast for image enhancement during stress echocardiography is cost-effective and reduces additional diagnostic testing. Am J Cardiol 2001;87:1430-2.
25 Nemes A, Geleijnse ML, Krenning BJ, et al. Usefulness of ultrasound contrast agent to improve image quality during real-time three-dimensional stress echocardiography. Am J Cardiol 2007;99: 275-8.
26. Bae RY, Belohlavek M, Tanabe K, et al. Rapid three-dimensional myocardial contrast echocardiography: volumetric quantification of nonperfused myocardium after intravenous contrast administration. Echocardiography 1999;16:357-65.