

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/37290> holds various files of this Leiden University dissertation

Author: Hoogslag, Georgette Elise

Title: Deformation imaging and three-dimensional echocardiography : implications on clinical management of patients with ischemic heart disease

Issue Date: 2016-01-26

CHAPTER 6

Assessment of Left Ventricular Excursion using
Three Dimensional Dobutamine Stress
Echocardiography to Identify Significant Coronary
Artery Disease

Georgette E. Hoogslag, Emer Joyce, Jeroen J. Bax, Nina Ajmone Marsan,
Victoria Delgado

Submitted



ABSTRACT

Aims: Quantitative three-dimensional (3D) dobutamine stress echocardiography (DSE) for myocardial ischemia detection may be an adjuvant to left ventricular (LV) wall motion analysis. The aim of the current study was to assess the association between 3D LV excursion at global level during DSE and presence of significant coronary artery disease (CAD) on coronary angiography.

Methods and results: 3D DSE was performed in 40 patients (67 ± 12 years, 68% male) who underwent subsequent coronary angiography (median 1.6 months later). Using 3D echocardiography, global LV excursion was measured (in a total of 680 segments) at rest and peak dose and change between stages was calculated (peak-rest = Δ global LV excursion). Significant CAD was defined as $>70\%$ stenosis on coronary angiography. In total, 25 patients (63%) demonstrated significant CAD on coronary angiography. At rest, global LV excursion was similar in patients with and without significant CAD (5.1 ± 0.2 vs. 5.0 ± 0.2 mm, $p=0.74$). However, patients with significant CAD demonstrated a worsening in global LV excursion from rest to peak stress (from 5.1 ± 0.2 to 4.1 ± 0.2 mm, $p<0.001$) while global LV excursion in patients without significant CAD remained unchanged (from 5.0 ± 0.2 to 5.5 ± 0.2 mm, $p=0.10$). After adjusting for clinically relevant characteristics, Δ global LV excursion was independently associated with significant CAD (odds ratio 0.29, 95% confidence interval 0.12–0.72, $p=0.008$).

Conclusion: Analysis of 3D echocardiographic LV excursion at global level on full protocol DSE may be a helpful tool to detect CAD on coronary angiography.

INTRODUCTION

Dobutamine stress echocardiography (DSE) has been widely used to detect and localize myocardial ischemia in patients with suspected coronary artery disease (CAD).¹⁻³ Detection of hemodynamically significant CAD relies on the assessment of changes in left ventricular (LV) wall motion and thickening between rest and at peak dose of dobutamine. However, this assessment is challenging, often highly subjective, requires training and is dependent on observer and image quality.^{4,5} Quantitative approaches using three-dimensional (3D) echocardiography may overcome these limitations. Three-dimensional echocardiography permits the acquisition of the LV full volume enabling comparison the same LV walls (or segments) on a tomographic approach between rest and peak dose of dobutamine and avoiding misalignments and foreshortening. In addition, in the last years, advances in semi-automated software to post-process the data have reduced observer dependence and novel quantitative parameters of LV mechanics (excursion and deformation) may permit objective detection of myocardial ischemia.⁶⁻⁸

Left ventricular (LV) excursion (or left atrioventricular plane displacement) is a surrogate of the LV longitudinal contraction that can be reduced during myocardial ischemia.⁹ Previous studies have shown the association between changes in LV excursion assessed during 2-dimensional DSE with the presence of significant CAD.¹⁰⁻¹³ However, the role of 3D LV excursion at global level in DSE for the detection of myocardial ischemia remains unexplored to date. Therefore, the aim of the current study was to evaluate the association between changes in LV excursion, assessed at global level, during full protocol 3D DSE and presence of significant CAD on coronary angiography in patients with suspected CAD.

METHODS

Patient population

Patients with suspected CAD who were referred for DSE and subsequently underwent invasive coronary angiography or multi-detector row computed tomography coronary angiography within 6 months after the DSE were included in the present evaluation. Patients with a recent acute coronary syndrome or recent revascularization, severe valvular disease or prosthetic valves, congenital heart disease, previous coronary artery bypass grafting and left bundle branch block or pacemaker rhythm were excluded. Clinical and echocardiographic data were collected at the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, The Netherlands) and the echocardiography database, respectively, and were retrospectively analyzed. Patients provided consent for the procedure.

Dobutamine stress protocol and image acquisition

Dobutamine stress echocardiography was performed according to current recommendations.^{2,14} Dobutamine was infused through a peripheral intravenous line with a starting dose of 5 or 10 µg/kg/min, after which the dose increased every 5 minutes up to 40 µg/kg/min. Blood pressure and 12-lead electrocardiogram were monitored at every stage of DSE. Three-dimensional echocardiographic data were acquired at baseline, low and peak dose dobutamine and at recovery. If necessary, intravenous atropine (up to 1 mg) was administered during the last stage of the DSE to achieve the target heart rate (defined as 85% of age-predicted maximal heart rate). Standard endpoints for DSE included target heart rate, extensive new wall motion abnormalities, ischemic ECG changes (>2mV ST-segment shift), severe angina, systolic blood pressure fall or rise and significant (supra-) ventricular arrhythmias.^{2,3} In patients with regional wall motion abnormalities at rest, a new or worsening wall motion abnormality (biphasic response) defined a positive test.

Three-dimensional images were obtained with the patient in the left lateral decubitus position using a commercially available system (iE33, Philips Medical Systems, Bothell, Washington, USA) equipped with an X5-1 fully sampled matrix array transducer. At rest, low dose and peak dose, apical 3D LV full-volume data sets were obtained during breath hold and were digitally stored. Four small real-time sub-volumes were acquired from alternate cardiac cycles and combined to provide a larger pyramidal volume (up to 103x103 degrees) and to ensure a complete capture of the LV. For the assessment of LV volumes and ejection fraction (LVEF), the lowest scan line density was used and gain and compression were adjusted to obtain a good image quality and a clearly defined endocardial border. Subsequently, 3D data analysis was performed offline using Q-Lab Version 9.0 (Philips Medical Systems).

Three-dimensional echocardiographic analysis

The apical 4- and 2-chamber views and the parasternal short-axis view were automatically displayed by the software. After manually indicating the mitral annulus by 4 points and the LV apex on both end-systolic and end-diastolic frames, the software automatically identified the entire endocardial border in each frame. If required, manual adjustment of the endocardial contour was possible. Subsequently, a 3D model was generated from which LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LVEF were automatically quantified. The papillary muscles were considered part of the LV cavity. For the calculation of global LV excursion at rest and peak stress, the results of the volume tracking analysis were exported in an Excel spreadsheet file. Subsequently, global LV excursion was noted for each segment and global LV excursion was calculated by averaging original segmental data (Figure 1). In addition, the change in global LV excursion between stages (peak-rest) was calculated (Δ global LV excursion).

Coronary angiography

Invasive coronary angiography was performed in 36 patients and the presence and the degree of CAD was assessed by computer-assisted quantitative coronary angiography using multiple planes. Multi-detector computed tomography coronary angiography was performed in 4 patients using a 320-row scanner (Acquilion ONE, Toshiba Medical Systems, Otaware, Japan). Significant CAD was defined as >70% luminal diameter stenosis in ≥ 1 of the 3 major epicardial vessels or associated large side branches.

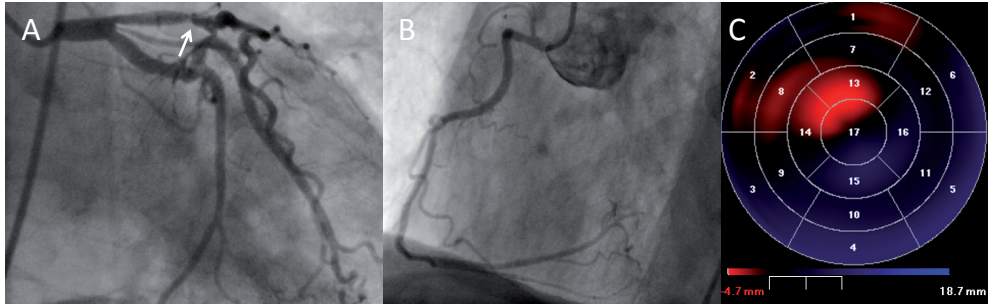


Figure 1. Example of a patient with a significant stenosis on coronary angiography of the left anterior descending artery. Panel A shows the angiography of the left coronary system with a significant proximal stenosis of the left anterior descending coronary artery. Panel B shows a right coronary artery without significant lesions. At peak stress dobutamine stress echocardiography, the polar map obtained from 3-dimensional LV full volume data shows reduced excursion of the LV segments supplied by the left anterior descending coronary artery (Panel C). The LV excursion is color-coded from red to blue indicating in red the segments with no excursion or lengthening and in blue the segments with preserved or enhanced excursion. In this example, the segments that present reduced excursion or lengthening at peak stress are the apical anteroseptal and anterior and the mid septal and anteroseptal.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation, mean $\pm$ standard error or as median and interquartile range, where appropriate. Categorical data are presented as absolute numbers and percentages. The Student's paired *t*-test was used to assess differences between stages for individual DSE parameters in the total patient population. Differences in DSE parameters between patients with and without significant CAD on coronary angiography across both stages (group stage interaction) were evaluated using linear mixed models. Moreover, differences within groups and differences between groups at each stage were evaluated. Logistic regression analysis was used to assess the relationship between significant CAD on coronary angiography and 3D LV excursion at global level. Variables with a *p*-value <0.10 in univariate analyses were entered in a multivariate model. In order to avoid overfitting the model the number of variables included were limited due to the number of patients with significant CAD. To avoid multicollinearity, a correlation coefficient of <0.7 was set.

All statistical tests were 2-sided and a p-value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

A total of 40 patients with analyzable 3D DSE data were included. Patients with atrial fibrillation during the DSE ($n=2$) and patients with poor image quality ($n=4$) were excluded. The clinical characteristics of the patients are summarized in Table 1. Mean age of the patient population was 67 ± 12 years and most patients were male (68%). Median time from DSE to coronary angiography was 1.6 (interquartile range 0.9–3.0) months. A total of 25 patients (63%) demonstrated significant CAD $>70\%$ in ≥ 1 epicardial vessel or associated large side branch (left anterior descending artery 50%; left circumflex artery 35%; right coronary artery 25%). Of the patients with significant CAD on coronary angiography, 11 (44%) had single-vessel disease, 9 (36%) had 2-vessel disease and 5 (20%) had 3-vessel disease.

DSE and 3D echocardiography

For the entire patient population, mean heart rates were 67 ± 10 and 128 ± 12 beats/minute at rest and peak stress, respectively. A total of 26 (65%) patients had a positive DSE based on wall motion analysis. A total of 656 segments (96%) and 661 segments (97%) were available at rest and peak stress, respectively, for the calculations of rest, peak and Δ global LV excursion. Mean frame rate at rest and peak stress were 24 ± 2 and 25 ± 3 frames/second, respectively. In the total population, from rest to peak dose significant decreases in LVEDV (from 94.2 ± 26.8 to 87.6 ± 24.9 mL, $p=0.002$), LVEF (from 54.3 ± 5.6 to $51.5 \pm 9.1\%$, $p=0.04$) and in global LV excursion (from 5.0 ± 0.9 to 4.6 ± 1.1 mm, $p=0.03$) were observed. However, LVESV did not change (from 43.3 ± 14.5 to 43.1 ± 17.9 mL, $p=0.88$).

Differences in 3D DSE parameters between patients with and without significant CAD on coronary angiography across stages are illustrated in Figure 2. At rest, patients with and without significant CAD showed comparable LV volumes (LVESV: 44.3 ± 2.9 vs. 41.7 ± 3.8 mL, $p=0.59$; LVEDV: 95.8 ± 5.4 vs. 91.6 ± 7.0 mL, $p=0.64$) and LV function (LVEF: 54.1 ± 1.1 vs. $54.6 \pm 1.5\%$, $p=0.81$; global LV excursion: 5.1 ± 0.2 vs. 5.0 ± 0.2 mm, $p=0.74$). In patients with significant CAD, LVESV increased from rest to peak stress (from 44.3 ± 2.9 to 48.1 ± 3.4 mL, $p=0.02$) while patients without significant CAD demonstrated a decrease in LVESV (from 41.7 ± 3.8 to 34.7 ± 4.4 mL, $p=0.005$). A significant difference was observed in changes in LVESV from rest to peak stress in patients with and without significant CAD (group stage interaction $p<0.001$). Also, LVEDV decreased in patients without significant CAD (from 91.6 ± 7.0 to 80.5 ± 6.4 mL, $p=0.02$). Patients with significant CAD demonstrated a trend towards a decrease in LVEDV (from 95.8 ± 5.4 to 91.8 ± 4.9 mL,

Table 1. Patient characteristics

	Total patient population (n=40)
Clinical characteristics	
Age (years)	67±12
Male gender, n (%)	27 (68%)
Medical history, n (%)	
Previous PTCA	10 (25%)
Previous myocardial infarction	6 (15%)
Current or previous smoking	21 (57%)
Diabetes	6 (15%)
Family history of CAD	17 (45%)
Hyperlipidemia	18 (45%)
Hypertension	23 (58%)
Medical therapy, n (%)	
ACE inhibitors/ARBs	25 (63%)
β-Blockers	26 (65%)
Statins	27 (68%)
Calcium antagonists	10 (25%)

Data are presented as mean ± standard deviation or as number (percentage).

ACE-inhibitor = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty.

$p=0.06$). In line, only a trend was observed in the difference in LVEDV changes between patients with and without significant CAD (group stage interaction $p=0.09$). Furthermore, patients with significant CAD showed a decrease in LV systolic function (LVEF: from 54.1 ± 1.1 to $47.9 \pm 1.6\%$, $p<0.001$) while in patients without significant CAD, LVEF demonstrated a trend towards improvement from rest to peak stress (from 54.6 ± 1.5 to $57.6 \pm 2.0\%$, $p=0.12$). Changes in LVEF from rest to peak dose across patient groups were different (group stage interaction $p<0.001$). Global LV excursion demonstrated the same pattern as LVEF: in patients with significant CAD, global LV excursion worsened (from 5.1 ± 0.2 to 4.1 ± 0.2 mm, $p<0.001$) while global LV excursion in patients without significant CAD showed a trend towards improvement (from 5.0 ± 0.2 to 5.5 ± 0.2 mm, $p=0.10$). A significant difference in changes in global LV excursion between patients with and without significant CAD was also observed (group stage interaction $p<0.001$).

Univariate and multivariate logistic regression analyses were performed to assess the association between the presence of significant CAD on coronary angiography and Δ global LV excursion. At univariate level, Δ global LV excursion was associated with

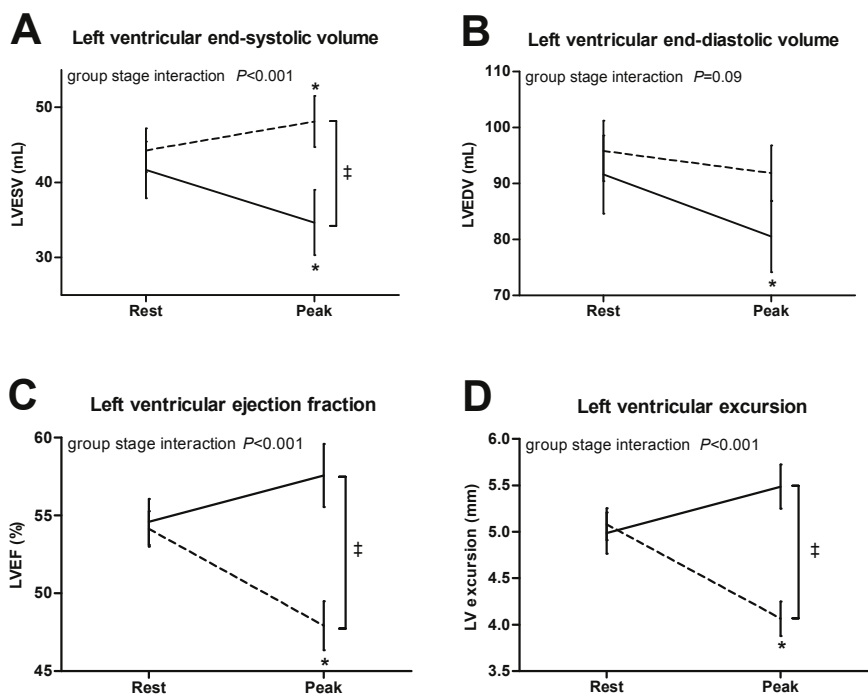


Figure 2. Three-dimensional dobutamine stress echocardiography analysis (LVESV, LVEDV, LVEF and global LV excursion) compared across patients with (dashed line) and without (solid black line) significant coronary artery disease on coronary angiography (defined as >70% stenosis). Group stage interaction p-values (differences in parameters between groups across both stages) are shown. * $p < 0.05$ compared to rest stage. # $p < 0.05$ between patients with and without significant coronary artery disease at that particular stage. LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

Table 2. Determinants of significant coronary artery disease on coronary angiography

	Multivariate analysis	
	OR (95% CI)	p
Age (years)	1.12 (1.01–1.24)	0.04
Systolic blood pressure at rest (mmHg)	1.03 (0.97–1.09)	0.30
Δglobal LV excursion (mm)	0.29 (0.12–0.72)	0.008

Significant CAD was defined on coronary angiography as >70% luminal diameter stenosis in ≥ 1 of the 3 major epicardial vessels or associated large side branches.
Δ = delta (peak-rest); CI = confidence interval; LV = left ventricular; OR = odds ratio.

significant CAD (odds ratio 0.28, 95% confidence interval 0.13–0.61, $p=0.001$). Other significant univariate parameters for the prediction of significant CAD were age, systolic blood pressure at rest, Δ systolic blood pressure, LVESV at peak, Δ LVESV, LVEF at peak, Δ LVEF and global LV excursion at peak. The final multivariate model included Δ global LV excursion, age and systolic blood pressure at rest (Table 2). In this model, Δ global LV excursion remained an independent determinant of significant CAD (odds ratio 0.29, 95% confidence interval 0.12–0.72, $p=0.008$; Table 2).

DISCUSSION

The present study evaluated the quantitative measure LV excursion at global level on 3D DSE in 40 patients with suspected CAD undergoing coronary angiography. At rest, global LV excursion was similar in patients with and without significant CAD. From rest to peak stress, however, patients with significant CAD demonstrated a decrease in global LV excursion while patients without significant CAD showed an improvement. Furthermore, after adjusting for clinically relevant parameters, change in global LV excursion from rest to peak stress was independently associated with the presence of significant CAD on coronary angiography. Therefore, 3D LV excursion at global level may be helpful in detecting the presence of significant CAD during full protocol DSE.

Quantitative analysis of DSE: 3D LV excursion

Detection of myocardial ischemia with conventional 2-dimensional DSE using visual detection of myocardial thickening and motion remains challenging and highly dependent on observer experience and image quality.^{4,5} Quantitative techniques based 3D echocardiography may overcome these limitations. Three-dimensional echocardiography minimizes the risk of foreshortened image acquisition improving the accuracy of this technique to detect ischemia in apical segments compared with 2-dimensional echocardiography.^{6–8} In addition, advances in post-processing softwares that provide quantitative parameters of LV mechanics permit objective detection of myocardial ischemia.

The longitudinal myocardial fibers, which are located in the subendocardium, are highly susceptible to ischemia and are therefore the first to be affected when hemodynamically significant coronary lesions exist. Consequently, quantifying longitudinal fiber function using LV excursion may be a helpful objective measure to detect myocardial ischemia in patients with suspected CAD. Previous studies used M-mode echocardiography to analyze the mitral plane displacement during systole toward the apex (left atrioventricular plane displacement).^{9,15–17} In a study by Rydberg et al evaluating 333 patients with stable CAD and abnormal coronary angiogram, LV excursion was associated with poor outcome in patients with significant CAD.¹⁸ In addition, LV excursion demonstrated a good correlation with global LV function measured by LVEF^{19,20} and with the degree and extent of CAD.²¹ Importantly, almost all patients with abnormal LV excursion but normal regional wall motion,

had some form of structural heart disease, including myocardial infarction, angina pectoris, hypertension and abnormal angiograms, suggesting at least a complementary role of LV excursion to visual wall motion assessment.²²

Prior studies applying LV excursion during exercise or DSE demonstrated a good correlation with the presence of CAD.^{10,12,13} In a study by Alam et al, 48 patients with stable angina without prior myocardial infarction and 20 age-matched healthy controls underwent 2-dimensional exercise echocardiography and coronary angiography.¹⁰ LV excursion was measured at the septal, anterior, lateral and posterior LV walls using M-mode from the 2- and 4-chamber views.¹⁰ At rest, LV excursion was comparable between groups while immediately post-exercise healthy subjects demonstrated an increase in LV excursion and patients with CAD showed a decrease.¹⁰ Cain et al calculated LV excursion for all individual LV segments using color tissue Doppler imaging on 2-dimensional echocardiography in 70 patients undergoing DSE and coronary angiography.¹¹ At rest, LV excursion was comparable between normal, ischemic, viable and scar segments.¹¹ Although all differently diagnosed segments increased in displacement from rest to peak stress, ischemic, viable and scar segments demonstrated at peak stress a significantly lower LV excursion compared to normal segments.¹¹

The current study evaluated LV excursion at global level based 3D volume tracking analysis. The feasibility of semi-automated quantitative volumetric analysis of 3D echocardiography was demonstrated by Corsi et al in rest images²³ and by Walimbe et al during stress echocardiography.²⁴ In line with those studies, the present evaluation demonstrated that global LV excursion at rest was not able to discriminate between patients with and without significant CAD confirmed on coronary angiography. Nevertheless, global LV excursion from rest to peak stress decreased in patients with significant CAD while in patients without significant CAD, global LV excursion improved. Importantly, change in global LV excursion from rest to peak stress was independently correlated with the presence of significant CAD. These results suggest that 3D LV excursion at global level could identify patients with significant CAD during full protocol DSE and may therefore be a useful quantitative tool in detecting CAD.

Limitations

The current study has several limitations. Firstly, because observational data were collected from one center, this study should be considered as hypothesis-generating and confirmation of the results in future studies is warranted, including larger patient populations from multiple centers and inclusion of patients with irregular heart rhythm and poor image quality. Furthermore, the small patient cohort precluded us from performing receiver operating characteristic curve analyses and analyzing data of 3D LV excursion per coronary territory.

CONCLUSIONS

Analysis of 3D echocardiographic LV excursion at global level on full protocol DSE may be a helpful tool to detect significant CAD on coronary angiography.

REFERENCES

- Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. *J Am Coll Cardiol* 1997;30:595-606.
- Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr* 2007;20:1021-41.
- Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D et al. Stress Echocardiography Expert Consensus Statement--Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J* 2009;30:278-89.
- Hoffmann R, Lethen H, Marwick T, Arnesen M, Fioretti P, Pingitore A et al. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. *J Am Coll Cardiol* 1996;27:330-6.
- Picano E, Lattanzi F, Orlandini A, Marini C, L'Abbate A. Stress echocardiography and the human factor: the importance of being expert. *J Am Coll Cardiol* 1991;17:666-9.
- Aggeli C, Giannopoulos G, Misovoulos P, Roussakis G, Christoforatou E, Kokkinakis C et al. Real-time three-dimensional dobutamine stress echocardiography for coronary artery disease diagnosis: validation with coronary angiography. *Heart* 2007;93:672-5.
- Ahmad M, Xie T, McCulloch M, Abreo G, Runge M. 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.
- Matsumura Y, Hozumi T, Arai K, Sugioka K, Ujino K, Takemoto Y 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.
- Alam M, Hoglund C, Thorstrand C, Philip A. Atrioventricular plane displacement in severe congestive heart failure following dilated cardiomyopathy or myocardial infarction. *J Intern Med* 1990;228:569-75.
- Alam M, Hoglund C, Thorstrand C, Carlens P. Effects of exercise on the displacement of the atrioventricular plane in patients with coronary artery disease. A new echocardiographic method of detecting reversible myocardial ischaemia. *Eur Heart J* 1991;12:760-5.
- Cain P, Baglin T, Khoury V, Case C, Marwick TH. Automated regional myocardial displacement for facilitating the interpretation of dobutamine echocardiography. *Am J Cardiol* 2002;89:1347-53.
- Duncan AM, O'Sullivan CA, Carr-White GS, Gibson DG, Henein MY. Long axis electromechanics during dobutamine stress in patients with coronary artery disease and left ventricular dysfunction. *Heart* 2001;86:397-404.
- Iwado Y, Mizushige K, Watanabe K, Ueda T, Furumoto W, Nozaki S et al. Quantitative analysis of myocardial response to dobutamine by measurement of left ventricular wall motion using omnidirectional M-mode echocardiography. *Am J Cardiol* 1999;83:765-9.
- Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D et al. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr* 2008;9:415-37.
- Hoglund C, Alam M, Thorstrand C. Atrioventricular valve plane displacement in healthy persons. An echocardiographic study. *Acta Med Scand* 1988;224:557-62.
- Hoglund C, Alam M, Thorstrand C. Effects of acute myocardial infarction on the displacement of the atrioventricular plane: an echocardiographic study. *J Intern Med* 1989;226:251-6.
- Lundback S. Cardiac pumping and function of the ventricular septum. *Acta Physiol Scand Suppl* 1986;550:1-101.
- Rydberg E, Erhardt L, Brand B, Willenheimer R. Left atrioventricular plane displacement determined by echocardiography: a clinically useful, independent predictor of mortality in patients with stable coronary artery disease. *J Intern Med* 2003;254:479-85.
- Alam M, Hoglund C, Thorstrand C, Hellekant C. Haemodynamic significance of the atrioventricular plane displacement in patients with coronary artery disease. *Eur Heart J* 1992;13:194-200.
- Pai RG, Bodenheimer MM, Pai SM, Koss JH, Adamick RD. Usefulness of systolic excursion of the mitral anulus as an index of left ventricular systolic function. *Am J Cardiol* 1991;67:222-4.
- Rydberg E, Willenheimer R, Erhardt L. Left atrioventricular plane displacement at rest is reduced in relation to severity of coronary artery disease irrespective of prior myocardial infarction. *Int J Cardiol* 1999;69:201-7.
- Willenheimer R, Rydberg E, Stagmo M, Gudmundsson P, Ericsson G, Erhardt L. Echocardiographic assessment of left atrioventricular plane displacement as a complement to left ventricular regional wall motion evaluation in the detection of myocardial dysfunction. *Int J Cardiovasc Imaging* 2002;18:181-6.

23. Corsi C, Lang RM, Veronesi F, Weinert L, Caiani EG, MacEneaney P et al. Volumetric quantification of global and regional left ventricular function from real-time three-dimensional echocardiographic images. *Circulation* 2005;112:1161-70.
24. Walimbe V, Garcia M, Lalude O, Thomas J, Shekhar R. Quantitative real-time 3-dimensional stress echocardiography: a preliminary investigation of feasibility and effectiveness. *J Am Soc Echocardiogr* 2007;20:13-22.

