ADVANCES IN THE EVALUATION OF CARDIOVASCULAR FUNCTION BY ECHOCARDIOGRAPHY

Attila Nemes

ISBN: 978-90-8559-308-9

Printed by Optima Grafische Communicatie, Rotterdam, the Netherlands

ADVANCES IN THE EVALUATION OF CARDIOVASCULAR FUNCTION BY ECHOCARDIOGRAPHY

Voortschrijdend inzicht bij de evaluatie van de cardiovasculaire functie middels echocardiografie

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
Rector Magnificus

Prof.dr. S.W.J. Lamberts

and in accordance with the decision of the Doctorate Board
The public defence shall be held on

Thursday June 28, 2007 at 9.00 h.

by

Attila Nemes
born at Szeged, Hungary

Doctoral Committee

Promotor:	Prof.dr. M.L. Simoons
Other members:	Prof.dr. N. de Jong
	Prof.dr. A.J.J.C. Bogers
	Dr. R.B.A. van den Brink
Copromotor:	Dr. F.J. ten Cate

Dorkának és Vikinek

For Dorka and Viki

Contents

.

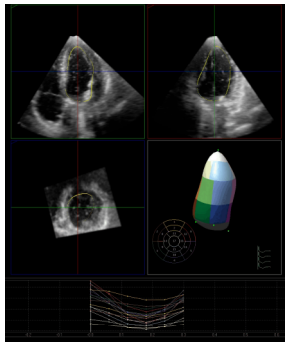
CHAPTER 1

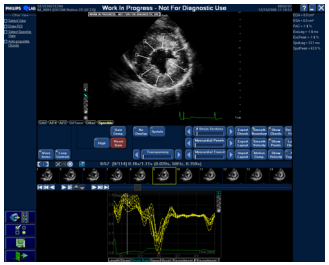
INTRODUCTION

Cardiovascular ultrasound has become the dominant non-invasive imaging technology in clinical cardiology. Its role has been established for the assessment of cardiovascular function at diagnosis and follow-up (Figure 1). Several different methods are available for the functional assessment of cardiac function and vascular elasticity, which includes stress echocardiography, contrast echocardiography and indirect vascular distensibility measurements. Recently, newer imaging modalities such as real-time 3-dimensional echocardiography and vascular imaging have increased the potential for the assessment and understanding of cardiac and vascular pathophysiology. This may become essential in the future for better initiation of therapy.

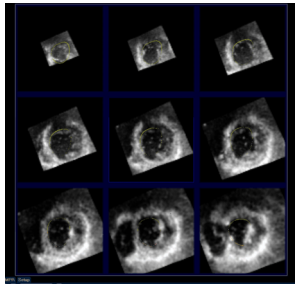
Stress echocardiography – From 2D to contrast 3D

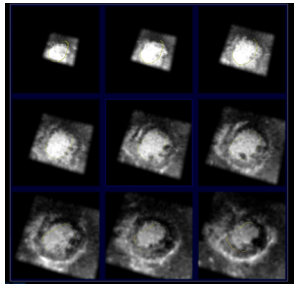
Two-dimensional (2D) stress echocardiography is a non-invasive stress modality indicated for the identification of coronary artery disease (CAD). The most important stress echocardiographic methods are exercise- (as physiologic) and pharmacologic- (non-physiologic) stress echocardiography. Regardless of the method applied, wall motion of left ventricular (LV) segments is compared at different levels of stress (for instance baseline, low-dose and peak dose at dobutamine stress) on several standardized LV views. The rationale for 2D stress echocardiography for detection of CAD is that cardiovascular stress will result in myocardial ischemia, manifested as a regional wall motion abnormality (1,2). Although the diagnostic and prognostic roles of 2D dobutamine stress echocardiography are well established, this stress modality suffers from a number of limitations. Suboptimal diagnostic accuracy may be caused by inadequate image quality, comparisons of non-identical LV wall



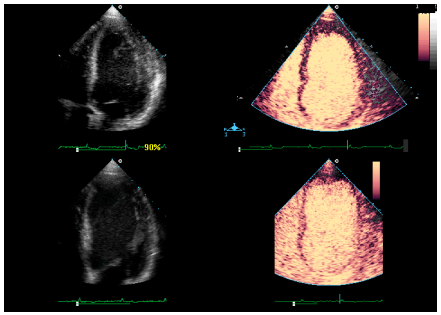


LV function
(2D, 3D)





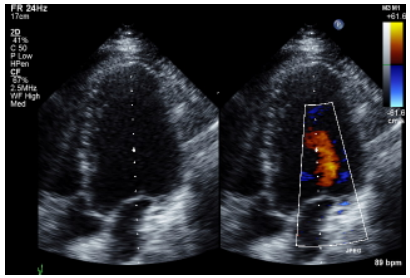
Detection of CAD
(stress 2D, 3D, contrast echo)

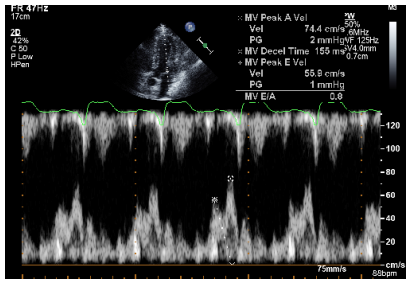


Perfusion
(contrast echo)

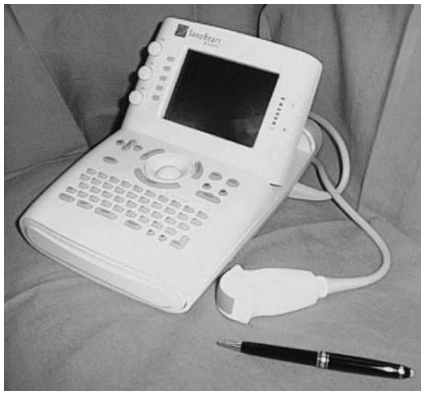
Cardiac Ultrasound

Valve evaluation
(Doppler, colour)

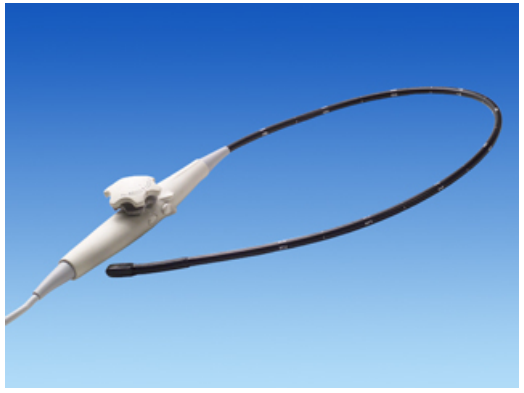




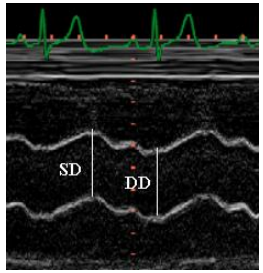
Versatility
(portable equipments)



Cardiac surgery
(transoesophageal echo)



Vasculature
(distensibility,
vasa vasorum)



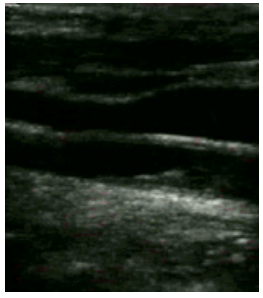


Figure 1

segments at rest, low-dose, and peak stress, and smaller ischemic areas may be missed in the limited available LV cross sections. The interpretation of this method is subjective with different existing definitions of abnormality and considerable inter-observer and inter-institutional diagnostic variability. The diagnostic accuracy of 2D dobutamine stress echocardiography can be increased by the use of ultrasound contrast agents.

Three-dimensional (3D) echocardiography has been advocated as the ultimate echocardiographic imaging modality since the start of the clinical application of echocardiography. Theoretically real-time three-dimensional echocardiography (RT3DE) as an ideal method for 3D echocardiography with online acquisition of a 3D dataset using matrix transducers (Figure 2).

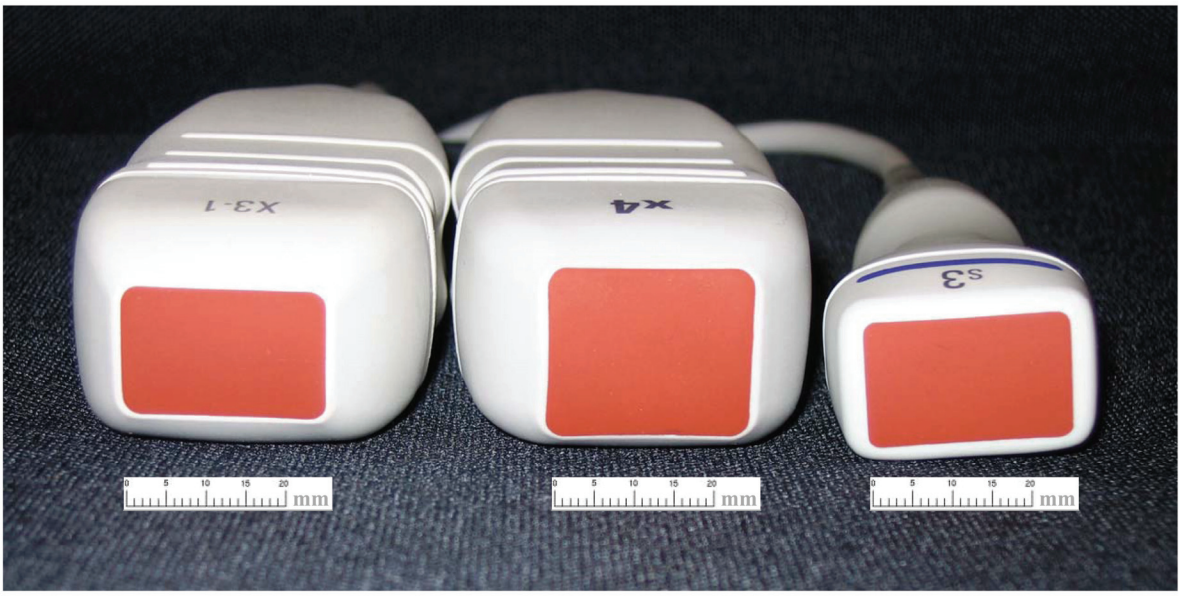


Figure 2 Size of the different 2D and 3D Philips transducers, from left to right: 3D-X3-1 (24 x 15 mm), 3D-X4 (24 x 20 mm) and 2D-S3 (24 x 15 mm).

Over the years several studies were published reporting the improved accuracy of RT3DE over 2D imaging for measurements and calculations of left ventricular volumes and masses.

Recent studies confirm the usefulness of newly developed software in the evaluation of regional volumes and systolic function for each segment from the RT3DE-derived 3D datasets. Theoretically, using RT3DE during stress testing its inherent advantages can eliminate some of the current limitations of stress 2D echocardiography, and may result in an improved diagnostic accuracy.

In the present thesis, our experience on stress 2D and contrast echocardiography and our first experience with dobutamine stress contrast-enhanced RT3DE to evaluate wall segments and their functions are reported. The optimal way for data acquisition during contrast stress RT3DE was determined. The current technical and clinical limitations of stress RT3DE are demonstrated, which need to be addressed before this method will become a reliable clinical tool in the daily practise of the practising cardiologist.

Aortic stiffness measurements

Recent studies have demonstrated that arterial stiffness is an independent risk factor and a predictor of cardiovascular mortality in a variety of diseases (3). Aortic stiffness is may be more important than conventional risk factors and an important factor affecting coronary perfusion. Direct measurement of arterial stiffness requires invasive techniques unsuitable for routine clinical practice. Several different non-invasive methods can be used for the characterization of aortic stiffness, most of them based on the direct measurement of the pulsatile change in aortic diameter and conventional left brachial arterial systolic and diastolic blood pressure measurement (4). With the knowledge of these parameters, a modulus/index can be calculated characterising vascular stiffness. Routine transthoracic echocardiography is a suitable method for the measurement of ascending aortic pulsatile change (Figure 3).

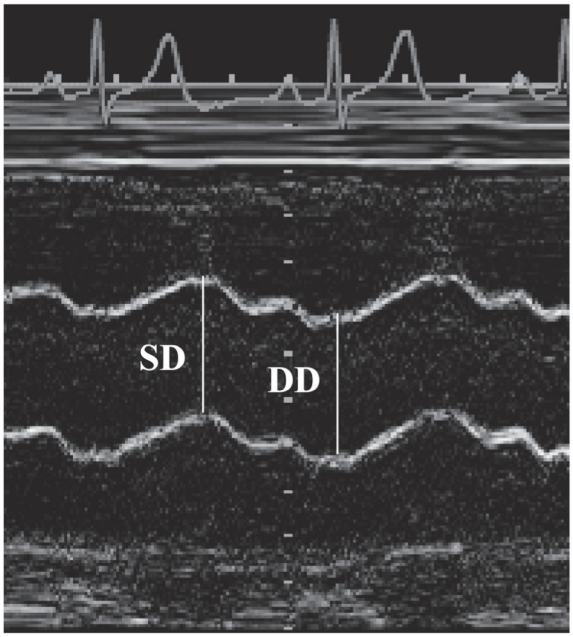


Figure 3 Measurements of systolic (SD) and diastolic (DD) diameters of the ascending aorta are shown on the M-mode tracing obtained at a level 3 cm above the aortic valve.

Storage diseases due to deposits can cause cardiac alterations, however, their effect on vascular elasticity has never been investigated. It is also known, that aortic valve stenosis is associated with vascular elasticity alterations, but long-term consequences of operation on aortic stiffness have not been examined. The role of newly developed RT3DE in the evaluation of regional vascular function was investigated.

References

1. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997;30:595-606.
2. Picano E, Mathias W, Jr., Pingitore A, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. Echo Dobutamine International Cooperative Study Group. Lancet 1994;344:1190-1192.
3. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236-1241.
4. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. Eur Heart J 1990;11:990-996.

Part A

Stress echocardiography –

From 2D to contrast 3D

CHAPTER 2

Factors Affecting Sensitivity and Specificity of Dobutamine Stress Echocardiography

submitted

Marcel L. Geleijnse

Boudewijn J. Krenning

Attila Nemes

Eric Boersma

Johan G. Bosch

Tjebbe W. Galema

Folkert J. ten Cate

Abstract

Background. Clinical characteristics of patients, angiographic referral bias and several technical factors may all affect the reported diagnostic accuracies of tests.

Aim of the study. To assess their influence on the diagnostic accuracy of dobutamine stress echocardiography (DSE).

Methodology. The medical literature from 1991 to 2001 was searched for diagnostic DSE studies and meta-analysis was applied to the 51 studies thus retrieved, including 5,739 patients. These studies were analyzed for year of publication, direct comparison with newer technologies, gender and mean age of patients, inclusion of patients with prior myocardial infarction, multi-vessel coronary disease, typical angina or beta-blocking medication, blinding of tests, definition of angiographic disease, angiographic referral bias, addition of atropine, definition of positive DSE and use of the biphasic response.

Results. DSE sensitivity was significantly related to the inclusion of patients with prior myocardial infarction (85% vs. 75%, P <0.0001) and defining DSE already positive in case of resting wall motion abnormalities rather than obligatory myocardial ischemia (86% vs. 80%, P <0.001). The presence of referral bias adversely affected DSE specificity (77% vs. 84%, P <0.005).

Conclusion. This analysis suggests that the reported sensitivity of DSE is higher and the specificity lower than that expected in clinical practice because of the inappropriate inclusion of patients with prior myocardial infarction, definition of positive DSE and the presence of referral bias.

Introduction

Dobutamine stress echocardiography (DSE) has been extensively studied as a diagnostic test for the prediction of coronary artery disease (CAD). However, sensitivities and specificities often differ greatly from one report to another. In one, often cited, review sensitivities ranged from 54% to 96% and specificities ranged from 62% to 93% (1). Recently, controversy has arisen regarding the inter-institutional stability of sensitivity and specificity and the wisdom of applying DSE results reported in the literature to other clinical laboratories (2). Clinical characteristics of patients, angiographic referral bias and several technical factors have all been implicated as causes of differences in reported diagnostic accuracies for other stress modalities such as exercise electrocardiography (3) and thallium scintigraphy (4). Therefore, we analyzed which factors influenced the sensitivity and specificity of DSE by applying meta-analysis on published diagnostic studies.

Methodology

Literature review. A Medline search for diagnostic DSE studies published up to 2001 using the terms “dobutamine stress” and “coronary artery disease” was performed. In addition, we reviewed the reference lists of review articles and eligible studies to complete the data search. Excluded from this search were reports solely reporting on patients with poor echocardiographic windows, left bundle branch block, hypertension and/or left ventricular hypertrophy or prior myocardial infarction. To avoid duplication of data only the largest report from an institution was considered, unless it was clear that different patients were included. The remaining 58 reports (5-53) were retained for review. One of these reports (51) described results of three separate study samples that had been based on different DSE protocols and these samples were treated as independent observations. For reports describing the value of atropine addition to DSE (27,33,36) only the dobutamine-atropine results were

considered for analysis. For reports describing the value of second harmonic imaging (49) only the fundamental imaging data were considered for analysis.

Statistical analysis. Sensitivity was defined as the number of true-positive tests divided by the total number of patients with angiographically significant CAD. *Specificity* was defined as the number of true-negative tests divided by the total number of patients without angiographically significant CAD. Since the study group sizes differed greatly (Table 1), all statistical tests were performed in a weighted fashion for testing sensitivities and specificities. Comparisons were performed using the standardized normal distribution test and the F-test. Multivariate analysis was performed by stepwise weighted linear regression. Statistical significance was defined at the $P < 0.05$ level and $F > 4.9$.

Recording the variables. The values of the variables were noted before recording the reported sensitivity and specificity. Two investigators (MLG and BJK) read the reports independently and recorded the variables listed in the Tables. When a disagreement occurred between the two investigators issues were resolved by consensus or a third investigator.

Discrete variables. These included the following: direct comparison with newer technologies (magnetic resonance imaging, three-dimensional echocardiography or tissue Doppler imaging), inclusion of patients with prior myocardial infarction, inclusion of patients with beta-blocking medication (for analysis no information on beta-blocking medication was interpreted as present), blind interpretation of DSE and coronary angiography (for analysis no information regarding blinding was interpreted as not blinded), definition of angiographic disease (50% versus 70% reduction in luminal diameter), presence of angiographic referral bias (DSE results influencing the decision to undergo coronary angiography), addition of

atropine, definition of positive DSE (dobutamine stress-induced or any wall motion abnormality), number of wall motion abnormalities required for a positive test (one or two segments, for analysis no information on the number of segments or statements like 'a wall motion abnormality' were interpreted as one segment), and use of the biphasic response (improvement of wall motion at low-dose followed by worsening of wall motion at high-dose, for analysis no information on use of the biphasic response was interpreted as not used).

Continuous variables. These included the following: year of publication, mean age, percentage of men, percentage of patients with prior myocardial infarction, percentage of patients with multi-vessel CAD, percentage of patients with a history of typical angina, percentage of patients receiving beta-blocking medication.

Results

Sensitivities and specificities (Table 1). For the 60 unique study groups in the 58 reports, 6,728 patients were studied with DSE and coronary angiography with sufficient data to record sensitivity and specificity. Of these, 4,621 had angiographic CAD whereas 2,107 did not. A total of 3,790 patients had true positive DSE resulting in a sensitivity of 0.820. There were 1,740 true negatives, allowing for a specificity of 0.826. Sensitivities and specificities for each of the 60 study groups are reported in Table 1.

Table 1. Group Characteristics Variables and Diagnostic Accuracies

Author	Year	Patients	Mean Age	Men (%)	Typical Angina (%)	CAD (%)	MVD CAD (%)
Afridi (5)	1994	45	62	99	-	84	69
Ahmad (6)	2001	90	-	47	32	64	41
Anthopoulos (7)	1996	120	75	60	43	74	58
Beleslin (8)	1994	136	50	85	36	88	8
Cain (9)	2001	114	62	75	-	74	47
Cohen (10)	1991	70	62	100	-	73	50
Dagianti (11)	1995	60	55	70	-	42	25
Daoud (12)	1995	76	60	58	-	86	55
Di Bello (13)	1996	45	53	73	87	84	42
Dionisopoulos (14)	1997	288	61	65	-	73	42
Elhendy (15)	1998	295	60	67	32	77	48
Epstein (16)	1992	61	59	70	-	89	48
Fathi (17)	2001	77	61	74	-	71	47
Gunalp (18)	1993	27	47	85	-	67	33
Hennessy (19)	1997	317	60	72	57	86	62
Ho (20)	1995	54	58	85	-	80	67
Ho (21)	1997	223	58	81	-	73	56
Hoffmann (22)	1993	60	57	77	-	80	35
Huang (23)	1997	93	61	77	-	72	52
Iwase (24)	1996	96	59	70	-	66	29
Kisacik (25)	1996	69	51	84	45	68	45
Lewis (26)	1999	92	58	0	-	27	16
Ling (27)	1996	183	69	35	-	81	60
Loimaala (28)	1999	60	55	67	65	73	30
Marcovitz (29)	1992	141	60	60	-	77	33
Martin (30)	1992	40	50	95	30	63	0
Marwick (31)	1993	217	58	72	65	65	34
Mazeika (32)	1992	50	54	88	-	72	48
McNeill (33)	1992	80	59	74	-	59	19
Nagel (34)	1999	172	60	71	-	63	41
Peteiro (35)	2001	41	63	78	-	78	49
Pingitore (36)	1996	110	60	83	-	84	46
Previtali (37)	1993	80	53	78	-	71	41
Sahin (38)	1994	65	58	71	71	65	40
Salustri (39)	1992	52	58	73	-	71	33
San Román (40)	1996	102	62	56	25	62	33
Santiago (41)	1994	77	67	70	-	69	0
Santoro (42)	1998	60	-	-	17	55	35
Sawada (43)	1991	55	59	62	19	64	25
Schröder (44)	1997	99	57	80	-	89	41
Senior (45)	1994	61	63	72	-	72	49
Slavich (46)	1996	46	59	0	-	48	26
Smart (47)	2000	183	60	73	26	65	32
Sochowski (48)	1995	46	58	67	48	54	28
Sozzi (49)	2001	64	59	70	-	77	55
Steinberg (50)	1997	120	67	99	-	72	46
Takeuchi (51)	1999	178	63	77	-	65	31
Takeuchi (51)	1999	249	64	80	-	55	33
Takeuchi (51)	1999	511	63	71	-	53	25
Vitarelli (52)	1997	59	52	64	-	81	44
Wu (53)	1996	30	58	84	-	57	40

CAD = Coronary Artery Disease. MI = Myocardial Infarction. MVD = Multi Vessel Disease. - = Not Available

Table 1. (Continued) Group Characteristics Variables and Diagnostic Accuracies

Author	Year	Beta-blocker	Beta-blocker (%)	MI	MI (%)	Sensitivity (%)	Specificity (%)
Afridi (5)	1994	Yes	27	Yes	29	71	86
Ahmad (6)	2001	Yes	40	Yes	25	59	81
Anthopoulos (7)	1996	Yes	46	Yes	40	87	84
Beleslin (8)	1994	Yes	43	Yes	57	82	76
Cain (9)	2001	Yes	52	Yes	8	88	80
Cohen (10)	1991	Stopped	0	Yes	27	86	95
Dagianti (11)	1995	Stopped	0	No	0	72	97
Daoud (12)	1995	Yes	12	Yes	37	92	73
Di Bello (13)	1996	Stopped	0	No	0	76	86
Dionisopoulos (14)	1997	Yes	31	Yes	-	87	89
Elhendy (15)	1998	Yes	35	Yes	52	75	87
Epstein (16)	1992	Yes	34	Yes	-	91	57
Fathi (17)	2001	Yes	32	Yes	42	98	59
Gunalp (18)	1993	Stopped	0	No	0	83	89
Hennessy (19)	1997	Stopped	0	Yes	39	86	60
Ho (20)	1995	-	-	Yes	41	93	73
Ho (21)	1997	Yes	-	Yes	39	94	79
Hoffmann (22)	1993	Stopped	0	No	0	79	83
Huang (23)	1997	Yes	58	Yes	39	93	77
Iwase (24)	1996	Stopped	0	Yes	30	79	88
Kisacik (25)	1996	Stopped	0	Yes	30	94	86
Lewis (26)	1999	Yes	22	Yes	10	40	94
Ling (27)	1996	Yes	23	Yes	32	95	51
Loimaala (28)	1999	Yes	20	Yes	15	95	63
Marcovitz (29)	1992	Yes	-	Yes	11	96	66
Martin (30)	1992	Yes	33	Yes	35	76	60
Marwick (31)	1993	Yes	19	No	0	72	83
Mazeika (32)	1992	Stopped	0	Yes	26	64	93
McNeill (33)	1992	Yes	80	Yes	35	70	88
Nagel (34)	1999	No	0	No	0	74	70
Peteiro (35)	2001	-	-	Yes	41	81	89
Pingitore (36)	1996	Yes	5	Yes	27	84	89
Previtali (37)	1993	Stopped	0	Yes	19	79	83
Sahin (38)	1994	Stopped	0	Yes	23	79	87
Salustri (39)	1992	Yes	69	Yes	27	54	80
San Román (40)	1996	Yes	21	No	0	78	95
Santiago (41)	1994	Stopped	0	Yes	-	79	67
Santoro (42)	1998	No	0	No	0	61	96
Sawada (43)	1991	Yes	51	No	0	89	85
Schröder (44)	1997	Stopped	0	Yes	53	89	82
Senior (45)	1994	Stopped	0	Yes	21	93	94
Slavich (46)	1996	Stopped	0	No	0	59	79
Smart (47)	2000	Yes	27	Yes	-	87	91
Sochowski (48)	1995	Yes	37	No	0	68	81
Sozzi (49)	2001	Yes	50	Yes	55	78	73
Steinberg (50)	1997	Stopped	0	Yes	23	87	91
Takeuchi (51)	1999	Yes	16	Yes	55	84	89
Takeuchi (51)	1999	Yes	18	Yes	48	85	83
Takeuchi (51)	1999	Yes	16	Yes	50	85	82
Vitarelli (52)	1997	Stopped	0	Yes	-	85	82
Wu (53)	1996	Yes	-	No	0	94	92

CAD = Coronary Artery Disease. MI = Myocardial Infarction. MVD = Multi Vessel Disease. - = Not Available

Effect of patient characteristics (Table 1).

Extend of CAD. In 47 studies sensitivity of single-vessel versus multi-vessel CAD could be calculated (mean sensitivity and specificity in these 5,464 patients was 0.819 and 0.836, respectively). In 1,606 patients with single-vessel CAD sensitivity was 0.738. In 2,144 patients with multi-vessel CAD sensitivity was 0.880 ($P < 0.0001$).

Prior myocardial infarction. The mean reported sensitivity and specificity from the 43 studies that included patients with prior myocardial infarctions were 0.840 and 0.819, respectively. For the 17 studies that excluded patients with prior myocardial infarctions sensitivity and specificity were 0.745 ($P < 0.001$) and 0.845, respectively. Of the continuous variables, the percentage of patients with prior myocardial infarction and resting wall motion abnormalities showed the highest correlation with DSE sensitivity (0.29 and 0.48, respectively). In the 780 myocardial infarction patients whose angiographic disease status and DSE result could be inferred from the available data, sensitivity was 0.829 and specificity was 0.764. In the 2,161 non-myocardial infarction patients whose angiographic disease status and DSE result could be inferred, sensitivity was 0.750 ($P < 0.0001$) and specificity was 0.856 ($P < 0.01$).

Other patient characteristics. Mean age, percentage of men and the use of beta-blocking medication did not significantly affect DSE sensitivity or specificity.

Effect of publication factors (Table 1). The years that studies were published were not correlated to DSE sensitivity or specificity

Effect of angiographic referral bias (Table 2). The presence of referral bias, present in 18 studies, negatively affected test specificity (0.781 vs. 0.826, $P < 0.005$). Its effect on sensitivity was not significant.

Table 2. Referral bias and other Angiographic Factors

Author	Referral Bias	Angiography Blinded	Angiography CAD% cut off	Angiography Quantitative
Afridi (5)	No	Yes	70	Yes
Ahmad (6)	No	-	50	No
Anthopoulos (7)	Yes	Yes	50	No
Beleslin (8)	Yes	Yes	50	Yes
Cain (9)	No	Yes	50	Yes
Cohen (10)	Yes	Yes	70	No
Dagianti (11)	Yes	Yes	70	Yes
Daoud (12)	No	-	50	No
Di Bello (13)	Yes	Yes	50	No
Dionisopoulos (14)	No	Yes	50	Yes
Elhendy (15)	No	-	50	Yes
Epstein (16)	No	Yes	50	No
Fathi (17)	No	Yes	50	Yes
Gunalp (18)	Yes	-	50	No
Hennessy (19)	Yes	Yes	50	No
Ho (20)	Yes	Yes	50	No
Ho (21)	Yes	-	50	Yes
Hoffmann (22)	Yes	Yes	70	Yes
Huang (23)	Yes	-	50	Yes
Iwase (24)	Yes	Yes	70	No
Kisacik (25)	Yes	Yes	50	No
Lewis (26)	Yes	Yes	50	Yes
Ling (27)	No	-	70	No
Loimaala (28)	Yes	-	50	No
Marcovitz (29)	No	-	50	Yes
Martin (30)	Yes	Yes	50	No
Marwick (31)	Yes	-	50	Yes
Mazeika (32)	Yes	Yes	70	No
McNeill (33)	Yes	-	50	No
Nagel (34)	Yes	Yes	50	No
Peteiro (35)	Yes	Yes	50	No
Pingitore (36)	Yes	Yes	50	Yes
Previtali (37)	Yes	Yes	50	No
Sahin (38)	Yes	Yes	50	No
Salustri (39)	Yes	Yes	50	Yes
San Román (40)	Yes	-	50	Yes
Santiago (41)	No	-	70	No
Santoro (42)	Yes	-	70	Yes
Sawada (43)	No	Yes	50	Yes
Schröder (44)	Yes	-	50	Yes
Senior (45)	Yes	Yes	50	No
Slavich (46)	Yes	-	50	Yes
Smart (47)	Yes	Yes	50	Yes
Sochowski (48)	Yes	Yes	50	No
Sozzi (49)	No	-	70	Yes
Steinberg (50)	Yes	Yes	70	No
Takeuchi (51)	Yes	Yes	50	Yes
Takeuchi (51)	Yes	Yes	50	Yes
Takeuchi (51)	Yes	Yes	50	Yes
Vitarelli (52)	No	-	70	No
Wu (53)	Yes	Yes	50	Yes

Abbreviation see Table 1.

Effect of technical angiographic factors (Table 2).

Definition of stenosis. There was no difference in diagnostic accuracy between the 45 studies in which 50% diameter stenosis was used as cut off for significant CAD compared to the 15 studies in which 70% diameter stenosis was used as cut off for significant CAD.

Blinding of reading. Blinding of the coronary angiogram, present in 40 studies, did not significantly affect sensitivity and specificity.

Quantitative scoring of stenosis. Quantitative scoring of the coronary angiogram, present in 33 studies, did not significantly affect sensitivity and specificity. In the 20 studies in which reading of the coronary angiogram was not blinded non-quantitative (visual) scoring did also not significantly affect sensitivity and specificity.

Effect of technical stress echocardiographic factors (Table 3).

Blinding of reading. Because DSE was in all but five studies blinded the effect of blinding could not be established.

Comparison with newer technologies. In the 12 studies assessing the value of newer technologies in direct comparison with DSE, sensitivity tended to be lower (0.794 vs. 0.833, P <0.10) and specificity was significantly lower (0.765 vs. 0.831, P <0.001).

DSE protocol. In the 17 studies in which resting wall motion abnormalities already constituted a positive DSE, sensitivity was higher compared to the 43 studies in which a dobutamine stress-induced wall motion abnormality (myocardial ischemia) was necessary to define DSE positive (0.863 vs. 0.788, P <0.001) with a loss in specificity (0.805 vs. 0.840, P <0.05). Addition of atropine, use of the biphasic response and the requirement of only one (versus two) ischemic segment for a positive DSE did not increase DSE sensitivity. When

Table 3. Stress Echocardiographic Factors

Author	Comparison with New Technology	Stress Echo Blinded	Dobutamine Dose	Atropine Addition	Definition of Positive Test	Segments Required	Biphasic Response
Afridi (5)	No	Yes	40	No	Rest or Stress	-	No
Ahmad (6)	Yes	Yes	40	Yes	Stress	-	-
Anthopoulos (7)	No	Yes	40	No	Stress	1	No
Beleslin (8)	No	Yes	40	No	Stress	1	-
Cain (9)	Yes	Yes	40	Yes	Rest or Stress	-	Yes
Cohen (10)	No	Yes	40	No	Stress	-	No
Dagianti (11)	No	Yes	40	No	Stress	1	-
Daoud (12)	No	-	30	No	Rest or Stress	1	No
Di Bello (13)	No	Yes	40	Yes	Stress	1	-
Dionisopoulos (14)	No	Yes	40	Yes	Rest or Stress	2	Yes
Elhendy (15)	No	Yes	40	Yes	Stress	1	Yes
Epstein (16)	No	Yes	50	No	Rest or Stress	1	-
Fathi (17)	Yes	Yes	40	Yes	Stress	-	Yes
Gunalp (18)	No	Yes	30	No	Stress	1	No
Hennessy (19)	No	Yes	50	Yes	Rest or Stress	2	-
Ho (20)	No	Yes	40	No	Stress	1	No
Ho (21)	No	Yes	40	Yes	Stress	2	No
Hoffmann (22)	No	Yes	40	Yes	Stress	-	No
Huang (23)	No	Yes	40	Yes	Rest or Stress	-	Yes
Iwase (24)	No	Yes	40	No	Stress	-	No
Kisacik (25)	No	Yes	40	Yes	Stress	1	No
Lewis (26)	No	Yes	40	Yes	Stress	1	Yes
Ling (27)	No	Yes	40	Yes	Rest or Stress	1	-
Loimaala (28)	No	Yes	40	No	Stress	1	-
Marcovitz (29)	No	Yes	30	No	Rest or Stress	-	No
Martin (30)	No	Yes	40	No	Stress	2	No
Marwick (31)	No	Yes	40	No	Rest or Stress	1	No
Mazeika (32)	No	Yes	20	No	Stress	1	No
McNeill (33)	No	Yes	40	Yes	Stress	1	No
Nagel (34)	Yes	Yes	40	Yes	Stress	1	Yes
Peteiro (35)	Yes	Yes	40	Yes	Rest or Stress	-	Yes
Pingitore (36)	No	Yes	40	Yes	Stress	1	No
Previtali (37)	No	Yes	40	No	Stress	1	No
Sahin (38)	No	Yes	30	No	Stress	1	No
Salustri (39)	No	Yes	40	No	Stress	1	No
San Román (40)	No	Yes	40	Yes	Stress	1	No
Santiago (41)	No	-	40	No	Rest or Stress	1	-
Santoro (42)	No	Yes	40	Yes	Stress	-	-
Sawada (43)	No	Yes	30	No	Stress	-	Yes
Schröder (44)	No	Yes	40	Yes	Stress	2	-
Senior (45)	No	Yes	40	No	Rest or Stress	-	-
Slavich (46)	No	Yes	40	Yes	Stress	1	-
Smart (47)	No	Yes	40	Yes	Rest or Stress	2	No
Sochowski (48)	No	Yes	40	No	Stress	-	-
Sozzi (49)	Yes	Yes	40	Yes	Stress	1	-
Steinberg (50)	No	Yes	40	No	Stress	1	No
Takeuchi (51)	No	Yes	30	No	Rest or Stress	1	-
Takeuchi (51)	No	Yes	40	No	Rest or Stress	1	-
Takeuchi (51)	No	Yes	40	Yes	Rest or Stress	1	-
Vitarelli (52)	No	-	50	No	Stress	1	Yes
Wu (53)	No	Yes	40	No	Stress	1	No

only the 43 studies that required myocardial ischemia for a positive DSE were included, atropine did also not increase sensitivity.

Multivariate analysis. At multivariate analysis, prior myocardial infarction ($F = 6.4$, $P < 0.001$) and definition of positive DSE ($F = 5.3$, $P < 0.01$) independently influenced sensitivity. Only the presence of referral bias ($F = 6.5$, $P < 0.005$) independently influenced specificity.

Discussion

This meta-analytical review indicates that patient characteristics, referral bias and technical factors (such as the definition of positive DSE) all significantly affect the reported sensitivity and specificity of DSE.

Patient characteristics. The inclusion of patients with prior myocardial infarction significantly increased the sensitivity of DSE. This may be the result of more extensive and/or severe CAD or the definition of positive DSE (see later). Since the diagnosis of CAD in patients with known prior myocardial infarction is nearly certain, the inclusion of such patients in investigations purporting to predict CAD seems inappropriate.

Ischemia during DSE is more likely in patients with more extensive CAD. This was confirmed by the significant relation between the number of diseased vessels and the likelihood of dobutamine-stress induced wall motion abnormalities. This finding confirms earlier reports (1) and support the use of DSE to identify patients at higher risk of multi-vessel CAD. The value of other CAD characteristics such as lesion severity (54,55), lesion type (56,57) or the presence of collaterals (56,58) could not be assessed because information concerning these variables was lacking in virtually all included diagnostic DSE studies.

We had expected that in studies which included patients on beta-blocking medication DSE sensitivity would be lower because dobutamine effects (predominantly mediated by beta-receptors) are obviously limited, resulting in a lesser increase in rate-pressure product (59, 60). Surprisingly, in these studies peak mean heart rate (uncorrected for age) was almost identical to studies that not included patients on beta-blocker (119 vs. 121 beats per minute) and consequently beta-blocker use did not affect DSE sensitivity. This latter finding may also be explained by more extensive and/or severe CAD in patients on beta-blockers (61) and the use of atropine in most of the studies including patients on beta-blockers (60). However, in studies in which atropine was not used, beta-blocker medication also did not result in a markedly lower peak mean heart rate (108 vs. 110 beats per minute) and consequently did not affect DSE sensitivity.

Unlike exercise electrocardiography (3) and exercise thallium scintigraphy (4), female gender did not affect DSE sensitivity or specificity. This finding is consistent with other publications focusing on the role of DSE in women (14, 62).

Referral bias. Referral bias is present when angiography is guided by results of the stress test under investigation. Because patients are predominantly send for coronary angiography with positive DSE this may increase sensitivity and decrease specificity of DSE. Unfortunately, regardless of study design it is almost impossible to completely avoid referral bias. Clearly, diagnostic DSE studies based on patients who are retrospectively selected because they underwent coronary angiography and DSE within a certain time frame (usually 6-12 weeks) will suffer from referral bias. However, prospective studies based on patients recruited from a coronary angiography waiting list are also not free from referral bias. These patients are usually listed because of some other positive stress test and thus are more likely to have a positive DSE. Finally, chest pain patients prospectively scheduled for coronary angiography

and DSE usually represent those with more serious complaints (typical angina rather than non-anginal chest pain) and are therefore not truly representative for the whole spectrum of patients encountered at the outpatient clinic. Nevertheless these limitations, those studies that attempted to avoid referral bias by not allowing the results of DSE to affect the decision to perform coronary angiogram had significantly higher specificities than studies that did not. Therefore, specificity in normal control patients will be somewhat higher than that obtained in most DSE studies.

Publication factors. We expected that technical advances would make sensitivity and specificity increase with time. However, we found no significant increase in test sensitivity between 1991 and 2001. Also, specificity was unaffected by time although this may be caused by the influence of referral bias in more recently published studies.

Stress echocardiographic technical factors. In studies in which rest wall motion abnormalities defined DSE already positive sensitivity was significantly higher. As mentioned before, since the diagnosis of CAD in patients with rest wall motion abnormalities is nearly certain, the inclusion of such patients in investigations purporting to predict CAD seems inappropriate.

Previous studies have shown that addition of atropine to dobutamine by increasing heart rate significantly increased DSE sensitivity without a loss in specificity (27, 33, 36). In our analysis, despite a very significant higher peak mean heart rate (130 vs. 109 beats per minute), the addition of atropine did not affect DSE sensitivity. Also, when we considered only DSE studies in which dobutamine stress-induced wall motion abnormalities (myocardial ischemia) were necessary for a positive DSE there was a tendency toward a higher DSE sensitivity in atropine studies.

Use of the biphasic response did not affect test sensitivity. Previous studies have shown that in patients with rest wall motion abnormalities use of the biphasic response significantly increased DSE sensitivity (63, 64). With respect to the biphasic response one problem is to determine exactly in which studies it was used. In one third of all studies it was unclear whether or not the biphasic response was used (Table 3). We assumed that the biphasic response was only used when it was clearly reported or could clearly be deducted. The validity of our conclusion that the biphasic response did not affect test sensitivity rests on this assumption. Another problem is that in some studies none of the patients had rest wall motion abnormalities and that in some studies including patients with rest wall motion abnormalities these latter already constituted a positive DSE. However, exclusion of these latter studies did not change our analysis.

Also, defining DSE positive in case of dobutamine stress-induced wall motion abnormality in one rather than two segments did not increase sensitivity of DSE. A previous study has shown that in particular in patients with prior myocardial infarction the use of at least two segments reduces sensitivity without a significant improvement in specificity (65). Our results may be different by our assumption that studies in which the description was unclear, the usual definition of the requirement of only one segment for a positive test was used.

Sensitivity and specificity of DSE were lower when the test was directly compared in the same patients with newer technologies such as dobutamine magnetic resonance imaging, three dimensional echocardiography or tissue Doppler imaging. It is an intriguing finding that for many stress modalities (i.e. stress radionuclide angiography) initially excellent results are reported, whereas in comparisons with newer tests results of the previously considered state-of-the-art test are not comparable to the initial reported results.

Other technical factors. When the result of one test influences the interpretation of another, a higher concordance between the two is expected. Since DSE reading was not blinded in only three studies we could not reliably assess the effect of non-blinding DSE. With respect to blinding of the coronary angiogram one problem is to determine exactly in which studies authors were blinded. Since the authors never reported the non-blinding of test analysis, we therefore assumed that studies used blinded analysis only when it was reported as such. In contradiction to reports on exercise thallium scintigraphy (4), blind reading of the coronary angiogram did not affect DSE sensitivity. Again, the validity of our conclusion that blinding does not affect DSE sensitivity significantly rests on this assumption.

Clinical and research applications. Clinicians should be aware of the expected diagnostic sensitivity and specificity of DSE. A large amount of data on this topic is available in the medical literature. However, one should always question whether these diagnostic accuracies obtained in top centers by experts in the field can be applied to your own clinical laboratory. Moreover, clinical characteristics of the patients studied, referral bias and several technical factors may all cause differences in diagnostic accuracies in real life. Our results indicate that the reported sensitivity of DSE is higher and the specificity lower than that expected in clinical practice because of the inappropriate inclusion of patients with prior myocardial infarction, definition of positive DSE and the presence of referral bias.

As stated many years ago by Detrano *et al.* (4), investigators in the field of diagnostic testing should more conform to methodological standards in conducting research and reporting their results (4, 66-68). Inappropriate patients such as those with prior myocardial infarction should be excluded or treated separately. Study groups should be explicitly defined, with careful description of patients characteristics and patients should not be excluded because they are expected to give false-positive or false-negative results. All tests (DSE and

coronary angiography) should be analyzed blindly, and referral bias should be avoided. Reviewers should use these standards in their criticisms and publication decisions. No report should be refused solely because the results are negative or disappointing since this practice has probably inflated the diagnostic accuracy of many tests.

References

1. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997;30:595-606.
2. Hoffmann R, Lethen H, Marwick T, et al. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. J Am Coll Cardiol 1996;27:330-336.
3. Hlatky MA, Pryor DB, Harrell FE, Jr., Califf RM, Mark DB, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis. Am J Med 1984;77:64-71.
4. Detrano R, Janosi A, Lyons KP, Marcondes G, Abbassi N, Froelicher VF. Factors affecting sensitivity and specificity of a diagnostic test: the exercise thallium scintigram. Am J Med 1988;84:699-710.
5. Afridi I, Quinones MA, Zoghbi WA, Cheirif J. Dobutamine stress echocardiography: sensitivity, specificity, and predictive value for future cardiac events. Am Heart J 1994;127:1510-1515.
6. Ahmad M, Xie T, McCulloch M, Abreo G, Runge M. Real-time three-dimensional dobutamine stress echocardiography in assessment stress echocardiography in assessment of ischemia: comparison with two-dimensional dobutamine stress echocardiography. J Am Coll Cardiol 2001;37:1303-1309.
7. Anthopoulos LP, Bonou MS, Kardaras FG, et al. Stress echocardiography in elderly patients with coronary artery disease: applicability, safety and prognostic value of dobutamine and adenosine echocardiography in elderly patients. J Am Coll Cardiol 1996;28:52-59.
8. Beleslin BD, Ostojic M, Stepanovic J, et al. Stress echocardiography in the detection of myocardial ischemia. Head- to-head comparison of exercise, dobutamine, and dipyridamole tests. Circulation 1994;90:1168-1176.
9. Cain P, Baglin T, Case C, Spicer D, Short L, Marwick TH. Application of tissue Doppler to interpretation of dobutamine echocardiography and comparison with quantitative coronary angiography. Am J Cardiol 2001;87:525-531.
10. Cohen JL, Greene TO, Ottenweller J, Binenbaum SZ, Wilchfort SD, Kim CS. Dobutamine digital echocardiography for detecting coronary artery disease. Am J Cardiol 1991;67:1311-1318.
11. Dagianti A, Penco M, Agati L, Sciomer S, Rosanio S, Fedele F. Stress echocardiography: comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. J Am Coll Cardiol 1995;26:18-25.
12. Daoud EG, Pitt A, Armstrong WF. Electrocardiographic response during dobutamine stress echocardiography. Am Heart J 1995;129:672-677.

13. Di Bello V, Bellina CR, Gori E, et al. Incremental diagnostic value of dobutamine stress echocardiography and dobutamine scintigraphy (technetium 99m-labeled sestamibi single-photon emission computed tomography) for assessment of presence and extent of coronary artery disease. J Nucl Cardiol 1996;3:212-220.
14. Dionisopoulos PN, Collins JD, Smart SC, Knickelbine TA, Sagar KB. The value of dobutamine stress echocardiography for the detection of coronary artery disease in women. J Am Soc Echocardiogr 1997;10:811-817.
15. Elhendy A, van Domburg RT, Poldermans D, et al. Safety and feasibility of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in diabetic patients unable to perform an exercise stress test. Diabetes Care 1998;21:1797-1802.
16. Epstein M, Gin K, Sterns L, Pollick C. Dobutamine stress echocardiography: initial experience of a Canadian centre. Can J Cardiol 1992;8:273-279.
17. Fathi R, Cain P, Nakatani S, Yu HC, Marwick TH. Effect of tissue Doppler on the accuracy of novice and expert interpreters of dobutamine echocardiography. Am J Cardiol 2001;88:400-405.
18. Gunalp B, Dokumaci B, Uyan C, et al. Value of dobutamine technetium-99m-sestamibi SPECT and echocardiography in the detection of coronary artery disease compared with coronary angiography. J Nucl Med 1993;34:889-894.
19. Hennessy TG, Codd MB, Kane G, McCarthy C, McCann HA, Sugrue DD. Dobutamine stress echocardiography in the detection of coronary artery disease: importance of the pretest likelihood of disease. Am Heart J 1997;134:685-692.
20. Ho FM, Huang PJ, Liau CS, et al. Dobutamine stress echocardiography compared with dipyridamole thallium- 201 single-photon emission computed tomography in detecting coronary artery disease. Eur Heart J 1995;16:570-575.
21. Ho YL, Wu CC, Lin LC, et al. Assessment of the functional significance of coronary artery stenosis by dobutamine-atropine stress echocardiography. Cardiology 1997;88:386-392.
22. Hoffmann R, Lethen H, Kleinhans E, Weiss M, Flachskampf FA, Hanrath P. Comparative evaluation of bicycle and dobutamine stress echocardiography with perfusion scintigraphy and bicycle electrocardiogram for identification of coronary artery disease. Am J Cardiol 1993;72:555-559.
23. Huang PJ, Ho YL, Wu CC, et al. Simultaneous dobutamine stress echocardiography and thallium-201 perfusion imaging for the detection of coronary artery disease. Cardiology 1997;88:556-562.
24. Iwase M, Fukui M, Tamagaki H, et al. Advantages and disadvantages of dobutamine stress echocardiography compared with treadmill exercise electrocardiography in detecting ischemia. Jpn Circ J 1996;60:954-960.
25. Kisacik HL, Ozdemir K, Altinyay E, et al. Comparison of exercise stress testing with simultaneous dobutamine stress echocardiography and technetium-99m isonitrile single-photon emission computerized tomography for diagnosis of coronary artery disease. Eur Heart J 1996;17:113-119.
26. Lewis JF, Lin L, McGorray S, et al. Dobutamine stress echocardiography in women with chest pain. Pilot phase data from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). J Am Coll Cardiol 1999;33:1462-1468.
27. Ling LH, Pellikka PA, Mahoney DW, et al. Atropine augmentation in dobutamine stress echocardiography: role and incremental value in a clinical practice setting. J Am Coll Cardiol 1996;28:551-557.

28. Loimaala A, Groundstroem K, Pasanen M, Oja P, Vuori I. Comparison of bicycle, heavy isometric, dipyridamole-atropine and dobutamine stress echocardiography for diagnosis of myocardial ischemia. Am J Cardiol 1999;84:1396-1400.
29. Marcovitz PA, Armstrong WF. Accuracy of dobutamine stress echocardiography in detecting coronary artery disease. Am J Cardiol 1992;69:1269-1273.
30. Martin TW, Seaworth JF, Johns JP, Pupa LE, Condos WR. Comparison of adenosine, dipyridamole, and dobutamine in stress echocardiography. Ann Intern Med 1992;116:190-196.
31. Marwick T, D'Hondt AM, Baudhuin T, et al. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy, or both? J Am Coll Cardiol 1993;22:159-167.
32. Mazeika PK, Nadazdin A, Oakley CM. Dobutamine stress echocardiography for detection and assessment of coronary artery disease. J Am Coll Cardiol 1992;19:1203-1211.
33. McNeill AJ, Fioretti PM, el-Said SM, Salustri A, Forster T, Roelandt JR. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. Am J Cardiol 1992;70:41-46.
34. Nagel E, Lehmkuhl HB, Bocksch W, et al. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. Circulation 1999;99:763-770.
35. Peteiro J, Monserrat L, Fabregas R, Manuel Vazquez J, Calvino R, Castro-Beiras A. Comparison of two-dimensional echocardiography and pulsed Doppler tissue imaging during dobutamine-atropine stress testing to detect coronary artery disease. Echocardiography 2001;18:275-284.
36. Pingitore A, Picano E, Colosso MQ, et al. The atropine factor in pharmacologic stress echocardiography. Echo Persantine (EPIC) and Echo Dobutamine International Cooperative (EDIC) Study Groups. J Am Coll Cardiol 1996;27:1164-1170.
37. Previtali M, Lanzarini L, Fetiveau R, et al. Comparison of dobutamine stress echocardiography, dipyridamole stress echocardiography and exercise stress testing for diagnosis of coronary artery disease. Am J Cardiol 1993;72:865-870.
38. Sahin M, Karakelleoglu S, Alp N, Atesal S, Senocak H. Diagnostic value of dobutamine stress echocardiography in coronary artery disease. Thorac Cardiovasc Surg 1994;42:285-289.
39. Salustri A, Fioretti PM, Pozzoli MM, McNeill AJ, Roelandt JR. Dobutamine stress echocardiography: its role in the diagnosis of coronary artery disease. Eur Heart J 1992;13:70-77.
40. San Roman JA, Vilacosta I, Castillo JA, et al. Dipyridamole and dobutamine-atropine stress echocardiography in the diagnosis of coronary artery disease. Comparison with exercise stress test, analysis of agreement, and impact of antianginal treatment. Chest 1996;110:1248-1254.
41. Santiago P, Vacek JL, Rosamond TL. Dobutamine stress echocardiography: clinical utility and predictive value at various infusion rates. Am Heart J 1994;128:804-808.
42. Santoro GM, Sciagra R, Buonamici P, et al. Head-to-head comparison of exercise stress testing, pharmacologic stress echocardiography, and perfusion tomography as first-line examination for chest pain in patients without history of coronary artery disease. J Nucl Cardiol 1998;5:19-27.
43. Sawada SG, Segar DS, Ryan T, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. Circulation 1991;83:1605-1614.

44. Schroder K, Agrawal R, Voller H, Kursten B, Dissmann R, Schultheiss HP. Factors influencing the diagnostic accuracy of dobutamine stress echocardiography. Int J Card Imaging 1997;13:493-498.
45. Senior R, Sridhara BS, Anagnostou E, Handler C, Raftery EB, Lahiri A. Synergistic value of simultaneous stress dobutamine sestamibi single- photon-emission computerized tomography and echocardiography in the detection of coronary artery disease. Am Heart J 1994;128:713-718.
46. Slavich GA, Guerra UP, Morocutti G, et al. Feasibility of simultaneous Tc99m sestamibi and 2D-echo cardiac imaging during dobutamine pharmacologic stress. Preliminary results in a female population. Int J Card Imaging 1996;12:113-118.
47. Smart SC, Bhatia A, Hellman R, et al. Dobutamine-atropine stress echocardiography and dipyridamole sestamibi scintigraphy for the detection of coronary artery disease: limitations and concordance. J Am Coll Cardiol 2000;36:1265-1273.
48. Sochowski RA, Yvorchuk KJ, Yang Y, Rattes MF, Chan KL. Dobutamine and dipyridamole stress echocardiography in patients with a low incidence of severe coronary artery disease. J Am Soc Echocardiogr 1995;8:482-487.
49. Sozzi FB, Poldermans D, Bax JJ, et al. Second harmonic imaging improves sensitivity of dobutamine stress echocardiography for the diagnosis of coronary artery disease. Am Heart J 2001;142:153-159.
50. Steinberg EH, Madmon L, Patel CP, Sedlis SP, Kronzon I, Cohen JL. Long-term prognostic significance of dobutamine echocardiography in patients with suspected coronary artery disease: results of a 5-year follow-up study. J Am Coll Cardiol 1997;29:969-973.
51. Takeuchi M, Miura Y, Sonoda S, Kuroiwa A. Comparison of Three Different Protocols for Dobutamine Stress Echocardiography: Does the Addition of Atropine Increase Complications, and Does It Improve Diagnostic Accuracy? Echocardiography 1999;16:347-355.
52. Vitarelli A, Luzzi MF, Penco M, Fedele F, Dagianti A. On-line quantitative assessment of left ventricular filling during dobutamine stress echocardiography: a useful addition to conventional wall motion scoring. Int J Cardiol 1997;59:57-69.
53. Wu CC, Ho YL, Kao SL, et al. Dobutamine stress echocardiography for detecting coronary artery disease. Cardiology 1996;87:244-249.
54. Arnese M, Salustri A, Fioretti PM, et al. Quantitative angiographic measurements of isolated left anterior descending coronary artery stenosis. Correlation with exercise echocardiography and technetium-99m 2-methoxy isobutyl isonitrile single-photon emission computed tomography. J Am Coll Cardiol 1995;25:1486-1491.
55. Baptista J, Arnese M, Roelandt JR, et al. Quantitative coronary angiography in the estimation of the functional significance of coronary stenosis: correlations with dobutamine- atropine stress test. J Am Coll Cardiol 1994;23:1434-1439.
56. Beleslin BD, Ostojic M, Djordjevic-Dikic A, et al. Integrated evaluation of relation between coronary lesion features and stress echocardiography results: the importance of coronary lesion morphology. J Am Coll Cardiol 1999;33:717-726.
57. Heyman J, Salvade P, Picano E, et al. The elusive link between coronary lesion morphology and dobutamine stress echocardiography results. The EDIC (Echo Dobutamine International Cooperative) Study Group. Int J Card Imaging 1997;13:395-401.
58. Elhendy A, Cornel JH, Roelandt JR, et al. Impact of severity of coronary artery stenosis and the collateral circulation on the functional outcome of dyssynergic myocardium after revascularization in patients with healed myocardial infarction and chronic left ventricular dysfunction. Am J Cardiol 1997;79:883-888.

59. Weissman NJ, Levangie MW, Guerrero JL, Weyman AE, Picard MH. Effect of beta-blockade on dobutamine stress echocardiography. Am Heart J 1996;131:698-703.
60. Fioretti PM, Poldermans D, Salustri A, et al. Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. Eur Heart J 1994;15:355-360.
61. Salustri A, Fioretti PM, McNeill AJ, Pozzoli MM, Roelandt JR. Pharmacological stress echocardiography in the diagnosis of coronary artery disease and myocardial ischaemia: a comparison between dobutamine and dipyridamole. Eur Heart J 1992;13:1356-1362.
62. Elhendy A, Geleijnse ML, van Domburg RT, et al. Gender differences in the accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery disease. Am J Cardiol 1997;80:1414-1418.
63. Senior R, Lahiri A. Enhanced detection of myocardial ischemia by stress dobutamine echocardiography utilizing the "biphasic" response of wall thickening during low and high dose dobutamine infusion. J Am Coll Cardiol 1995;26:26-32.
64. Elhendy A, Cornel JH, Roelandt JR, et al. Relation between contractile response of akinetic segments during dobutamine stress echocardiography and myocardial ischemia assessed by simultaneous thallium-201 single-photon emission computed tomography. Am J Cardiol 1996;77:955-959.
65. Elhendy A, van Domburg RT, Bax JJ, et al. Optimal criteria for the diagnosis of coronary artery disease by dobutamine stress echocardiography. Am J Cardiol 1998;82:1339-1344.
66. Philbrick JT, Horwitz RI, Feinstein AR, Langou RA, Chandler JP. The limited spectrum of patients studied in exercise test research. Analyzing the tip of the iceberg. Jama 1982;248:2467-2470.
67. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. N Engl J Med 1985;313:793-799.
68. Diamond GA. Monkey business. Am J Cardiol 1986;57:471-475.

CHAPTER 3

Incidence, Pathophysiology and Treatment of Complications During Dobutamine - Atropine Stress Echocardiography

submitted

Marcel L. Geleijnse

Boudewijn J. Krenning

Attila Nemes

Folkert J. ten Cate

Maarten L. Simoons

Jos R.T.C. Roelandt

Abstract

Background. Today's aggressive dobutamine-atropine stress echocardiography (DASE) protocol and expanding indications with inclusion of sicker patients have raised concerns about the safety of this stress modality.

Aim of the study. To investigate the incidence of complications during DASE and to provide pathophysiological insight and treatment options.

Methods. A MedLine search on studies reporting complications during DASE was performed with the search terms "*safety*", "*complication*", "*side effect*" or "*adverse effect*" in the Title. Data on incidence of complications were tabulated and calculated as mean percentage and range. Also, case reports describing complications were identified.

Results. Nineteen DASE safety studies with over 400 patients, including a total of 31 724 patients, were identified. Life-threatening complications (death, cardiac rupture, myocardial infarction, cerebrovascular accident, asystole, ventricular fibrillation and sustained ventricular tachycardia) occurred in approximately each one of 400 patients. This complication rate was in particular driven by the occurrence of sustained ventricular tachycardia, exclusion of this specific complication resulted in a complication rate of one in 1 000 tests. Death was only once reported in the safety studies due to ventricular fibrillation, but three times in case reports due to cardiac rupture after a recent inferior myocardial infarction. Patients with a history of myocardial infarction and/or impaired left ventricular function had a four times higher risk of cardiac rupture, ventricular fibrillation or myocardial infarction. Some of the most important complications did occur up to one hour after dobutamine discontinuation.

Conclusions. DASE carries a definite, albeit small, risk. This risk should always be carefully weighted against the expected diagnostic or prognostic benefit.

Introduction

Dobutamine stress echocardiography was clinically introduced in the mid-eighties (1). Indications for this stress modality rapidly expanded from diagnosing coronary artery disease (CAD) into risk stratification of patients undergoing vascular surgery, patients with chronic coronary artery disease, unstable angina, acute or chronic myocardial infarction (MI) or valvular heart disease as well as the assessment of myocardial viability in patients with severe left ventricular dysfunction. Thus, dobutamine stress has been applied to progressively more complex, older and higher risk patients. Additionally, stress protocols became more aggressive, with higher dobutamine doses in combination with atropine (2). Although generally regarded as a safe stress modality, serious complications do occur. In this review we will describe the incidence, pathophysiology and treatment of complications induced by dobutamine-atropine stress echocardiography (DASE).

Methods

A MedLine search on dobutamine stress echocardiography studies reporting complications was performed with the search terms *"dobutamine stress" and* "*safety*" or "*complication*" or "*side effect*" or "*adverse effect*" in the Title. By this initial search 47 studies were identified. From this initial search we excluded studies using other imaging modalities (magnetic resonance imaging, nuclear perfusion, transesophageal echocardiography), those specifically addressed to safety in specific patients (valvular heart disease, transplant patients, left ventricular thrombus, aneurysm, internal cardiac defibrillator). Also excluded were studies limited by a small number (<400) of patients because such smaller studies are more likely to be influenced by publication bias. Additional safety papers were included after screening the references of the selected studies and by the authors' extensive own knowledge. To avoid duplication of data only the largest report from a single centre was included. Data on

Table 1. Dobutamine-Atropine Stress Echocardiography Safety Reports

	Mertes (3)	Picano (4)	Pellikka (5)	Zahn (6)	Hiro (7)	Lamisse (8)	Pinton (9)
Year of publication	1993	1994	1995	1996	1997	1997	1997
Stress protocol	40 / 1[#]	40 / 1	50 / 2[#]	50 / 1	40 / 1	40 / 1	50 / 0
Number of patients	1 118	2 949	1 000	1 000	732	600	735
History of MI	33.5%	69.0%	NA	21.5%	NA	21.2%	NA
Mean age (yrs)	60	56	69	59	62	62	57
Complications							
Death	-	-	-	-	-	-	-
Cardiac rupture	-	-	-	-	-	-	-
MI	-	0.07%	0.10%	-	-	-	-
Cerebrovascular accident	-	-	0.10%	-	-	-	-
Atropine intoxication	-	0.17%	-	-	-	-	-
Asystole	-	-	-	-	-	-	-
Atrioventricular block	0.63%	NA	NA	0.10%	NA	NA	0.68
Ventricular arrhythmias							
Ventricular fibrillation	-	0.07%	-	0.10%	-	-	-
Ventricular tachycardia							
- sustained	-	0.07%	0.40%	-	-	0.54%	-
- nonsustained	3.6%	NA	5.6%	1.8%	NA	1.1%	0.5%
Premature ventricular complex	15.4%	NA	18.9%	7.1%	NA	8.0%	11.8%
Supraventricular arrhythmias							
Supraventricular tachycardia	3.4%	NA	7.0%	0.3%	NA	0.4%	0.0%
Atrial fibrillation or flutter	0.7%	NA	2.2%	1.0%	NA	1.1%	0.3%
Premature atrial complex	7.7%	NA	NA	NA	NA	5.6%	3.8%
Hypotension	3.2%	2.1%	2.9%	2.5%	3.6%	0.3%	0.8%
Hypertension	0.9%	0.8%	1.3%	1.0%	NA	2.6%	3.5%
Side effects	3.2%	2.4%	3.0%	4.4%	NA	1.0%	3.1%
Wall motion abnormalities	2.9%	NA	10.6%	10.0%	NA	0.0%	9.0%

	Hennesy (10)	Secknus (11)	Bremen (12)	Pezzano (13)	Plonska (14)	Mathias (15)
Year of publication	1997	1997	1998	1998	1999	1999
Stress protocol	50 / 1	40 / 2	40 / 1	40 / 1	40 / 1	40 / 1
Number of patients	474	3 011	1 035	3 041	582	4 033
History of MI	40.9%	15.8%	25.8%	63.0%	-	22.7%
Mean age (yrs)	59	66	69	58	52	56
Complications						
Death	-	-	-	-	-	-
Cardiac rupture	-	-	-	-	-	-
MI	-	0.03%	-	-	-	0.02%
Cerebrovascular accident	-	0.03%	-	-	-	-
Atropine intoxication	-	-	-	-	-	0.12%
Asystole	-	-	-	0.03%	-	-
Atrioventricular block	NA	NA	NA	0.03%	0.17%	0.40%
Ventricular arrhythmias						
Ventricular fibrillation	-	-	0.10%	0.07%	-	0.02%
Ventricular tachycardia						
- sustained	0.21%	0.17%	0.10%	-	-	0.20%
- nonsustained	1.7%	2.3%	7.3%	2.1%	1.0%	3.5%
Premature ventricular complex	NA	8.0%	NA	33.7%	4.6%	31.2%
Supraventricular arrhythmias						
Supraventricular tachycardia	3.0%	1.7%	NA	1.6%	-	0.9%
Atrial fibrillation or flutter	1.1%	1.1%	1.9%	0.5%	0.5%	0.8%
Premature atrial complex	NA	NA	NA	8.6%	1.2%	9.5%
Hypotension	0.2%	3.7%	1.6%	0.2%	7.6%	0.4%
Hypertension	0.2%	0.8%	0.9%	0.4%	2.6%	1.5%
Side effects	-	1.5%	5.1%	0.5%	0.7%	NA
Wall motion abnormalities	NA	0.9%	6.3%	NA	19.8%	NA

	Takeuchi (16)	Poldermans (17)	Chenzbraun (18)	Hirano (19)	Cortigiani (20)	Rodríguez (21)
Year of publication	1999	1999	1999	2001	2001	2001
Stress protocol	40 / 1[#]	40 / 1	50 / 1	40 / 0	40 / 1[#]	40 / 0
Number of patients	1 090	1 659	400	897	636	6 832
History of MI	50.4%	42.5%	NA	NA	NA	NA
Mean age (yrs)	63	62	67	NA	60	NA
Complications						
Death	-	-	-	-	-	0.01%
Cardiac rupture	-	-	-	-	-	0.01%
MI	0.09%	0.09%	-	-	-	0.06%
Cerebrovascular accident	-	-	-	-	-	0.01%
Atropine intoxication	-	-	-	-	-	-
Asystole	-	-	-	-	-	-
Atrioventricular block	0.28%	NA	0.25%	NA	NA	0.03%
Ventricular arrhythmias						
Ventricular fibrillation	-	0.18%	-	-	-	0.04%
Ventricular tachycardia						
- sustained	0.09%	0.78%	0.25%	-	0.31%	0.13%
- nonsustained	0.8%	2.7%	NA	NA	1.3%	NA
Premature ventricular complex	43.6%	NA	NA	34.1%	NA	NA
Supraventricular arrhythmias						
Supraventricular tachycardia	0.2%	NA	NA	NA	NA	NA
Atrial fibrillation or flutter	0.6%	1.5%	0.5%	NA	0.3%	NA
Premature atrial complex	27.8%	NA	NA	NA	NA	NA
Hypotension	0.4%	0.36%	7.0%	NA	0.8%	NA
Hypertension	NA	0.2%	3.5%	NA	0.6%	NA
Side effects	NA	0.2%	4.0%	NA	NA	NA
Wall motion abnormalities	32.0%	0.2%[*]	-	NA	NA	NA

NA = Not Available. * = Obtained by a prior smaller safety study from the same author (81). # = Patients within an early, initial timeframe underwent DASE without atropine. Stress protocol displayed as: dobutamine dose in µg/kg/minute / atropine dose in mg.

incidence of complications were thus obtained from nineteen studies (3-21), for a total of 31724 patients (Table 1). All these included studies fulfilled the final inclusion criterion of reporting at least the major complications death, acute MI, ventricular fibrillation and sustained ventricular tachycardia. For each study, death and the life-threatening complications cardiac rupture, acute MI, cerebrovascular accident, asystole, ventricular fibrillation and sustained ventricular tachycardia were noted. Other complications noted were atropine intoxication, atrioventricular (AV) block, supraventricular arrhythmias (regular supraventricular tachycardia, atrial fibrillation and atrial flutter), hypotension and hypertension. In addition, the incidence of wall motion abnormalities and hypotension and hypertension as a test endpoint was noted. To assure the quality of data extraction this was independently done by two physicians (MLG, BJK). All calculations on cumulative (mean) complication risks were done according to a weighted analysis in which the total number of patients with a complication was divided by the total number of patients at risk for a complication. Also, references were given to case reports and studies specifically dealing with a particular complication.

POTENTIALLY LIFE-THREATENING COMPLICATIONS

Death

Incidence: Less than 0.01% (0.003%, range 0.00 to 0.01%). Case reports (22-24).

Pathophysiology: In DASE safety studies death was only once reported due to ventricular fibrillation (21). In three case reports lethal cases of cardiac rupture were described (22-24).

Treatment: See other specific sections for treatment of potentially fatal complications.

Cardiac Rupture

Incidence: Less than 0.01% (0.003%, range 0.00 to 0.01%). Case reports (22-25).

Pathophysiology: Cardiac rupture was reported in five patients undergoing DASE with akinetic or dyskinetic inferior myocardium resulting from a recent (4-12 days old) inferior MI. In all five cases, the patient suddenly developed (atypical) chest pain and lost consciousness with pulseless electromechanical dissociation. In three of five patients cardiac rupture was fatal (22-24). Strong inotropic stimulation of necrotic and thinned myocardium may increase wall stress to such an extent that rupture results in that part of the myocardial wall with the least resistance. Of note, low-dose dobutamine provides already strong inotropic stimulation, as was shown in two case reports with ruptured myocardium at doses of only 10 μg/kg/min (22,25). Whether the inferior myocardial wall is more prone to rupture is controversial (26,27). Diagnosis should be easy by looking for sudden development of pericardial effusion.

Treatment: Discontinue dobutamine infusion. Emergency pericardiocentesis and surgery.

Myocardial Infarction

Incidence: 0.03% (range 0.00 to 0.10%). Case reports (28-33).

Pathophysiology: DASE may cause MI through different mechanism. In a coronary artery with an unstable atherosclerotic plaque, increment of heart rate and contractility may mechanically increase shear forces resulting in plaque disruption and thrombosis. Additionally, dobutamine has been shown to induce platelet activation and aggregation (34) and α_1-mediated coronary vasoconstriction, which may even paradoxically be exacerbated by administration of a non-selective β-blocker (see section on coronary spasm). Dobutamine stress-induced expansion of a sinus of Valsalva aneurysm, with compression of a coronary artery, was once reported as a potential mechanism for MI (32).

Treatment: Discontinue dobutamine infusion. Consider immediate coronary angiography followed by angioplasty or thrombolysis (35).

Cerebrovascular Accident

Incidence: Less than 0.01% (0.009%, range 0.00 to 0.10%). Complication specific publication (36).

Pathophysiology: DASE may cause a cerebrovascular accident through different mechanism. Increment of heart rate and blood pressure may mechanically increase shear forces across an aneurysmal arterial wall leading to haemorrhagic stroke (36). Ischemic stroke (including transient ischemic attack) may be caused by the same mechanisms as described in the previous section on MI. Additionally, ischemic stroke may occur in the setting of dobutamine stress-induced hypotension (see later) in the presence of a high-grade carotic artery stenosis (5).

Treatment: Discontinue dobutamine infusion. Hospitalisation in stroke unit. Consider immediate imaging with magnetic resonance imaging or computed tomography and thrombolysis (37).

Cardiac Asystole

Incidence: Less than 0.01% (0.003%, range 0.00 to 0.03%). Case reports (38-40).

Pathophysiology: The syndrome of sinus bradycardia with or without hypotension is well known during DASE. Eventually this may lead to asystole lasting 6-8 seconds (13,38). Although in an early report sinus node deceleration was linked to ischemia in the inferior myocardial wall (41), a powerful cardio-inhibitory vagal reflex seems a more likely mechanism. This reflex, known as the Bezold-Jarisch reflex, is a neurally mediated mechanism in which vigorous myocardial contraction stimulates intramyocardial mechanoreceptors, resulting in sympathetic withdrawal and enhanced parasympathetic activity (42). Alternatively, it was suggested that prohibition of oral intake before DASE may lead to volume depletion, and experimental data have demonstrated that in presence of a reduced cardiac volume β_1-adrenergic stimulation can elicit paradoxical bradycardia (43). In contradiction to the earlier

described life-threatening complications, patients with asystole usually had good baseline left ventricular function with a hyperdynamic response to dobutamine and usually absence of myocardial ischemia (38-40).

Treatment: Discontinue dobutamine infusion. Immediate intravenous bolus of atropine (0.5-2 mg).

Ventricular Fibrillation

Incidence: 0.04% (range 0.00 to 0.18%). Case reports (33,44-46).

Pathophysiology: All but two patients (15,33) described in the literature with available data had impaired left ventricular function and all had evidence for (usually severe) myocardial ischemia at DASE (4,6,15,44-47). Furthermore, except for one patient with ST-segment elevation, non-significant CAD and suspected coronary spasm (46), all patients who underwent coronary angiography showed left main or three-vessel CAD (4,6,12,33). So, ventricular fibrillation seems mainly to occur in patients with structural heart disease (presence of persistent factors such as scar tissue) in combination with inducible, dynamic factors such as severe and/or extensive myocardial ischemia and possibly electrolyte disturbances (see also next section on other ventricular arrhythmias).

Treatment: Discontinue dobutamine infusion. Cardiopulmonary resuscitation was in all but one patient (21) successful.

Sustained Ventricular Tachycardia

Incidence: 0.16% (range 0.00 to 0.78%). Complication specific publications (48-50). Case reports (51-53).

Pathophysiology: Dobutamine may provoke ventricular arrhythmias by several mechanism. Dobutamine has differential effects on action potential duration (54), QRS-duration and QTc-

interval (55) in normal and ischemic myocardium. The abnormal dispersion of conduction in adjacent areas of ischemic and non-ischemic myocardium thus created may be important in β-receptor mediated (re-entry) arrhythmogenesis. Additionally, dobutamine may increase intracellular calcium concentration by second messenger cyclic adenosine monophosphate (56). Increased intracellular calcium has been shown to increase automaticity in ventricular myocardium, and provoke triggered activity in the form of delayed afterdepolarizations (57). Finally, β-receptor stimulation reduces plasma potassium level, which may temporarily predispose patients to ventricular arrhythmias (58). Many safety studies have analysed clinical predictors for these arrhythmias. Ventricular arrhythmias have quite consistently been related to impaired left ventricular function (16,17,47-50,59) and a history of ventricular arrhythmias (47,49,59) but not to atropine addition (11,21,47,49,50) or myocardial ischemia (11,13,17,18,21,47-50,60). It should be noticed, however, that none of these studies made a distinction between non-sustained and sustained ventricular arrhythmias (probably because of the small number of the latter) and the incidence of ventricular tachycardias may be overestimated because of difficulties in differentiation with supraventricular tachycardia with aberration (48).

Treatment: Discontinuation of dobutamine infusion (ventricular arrhythmias are usually brief and self terminating). Intravenous β-blocker (metoprolol 5-10 mg over a 5-minute period). Intravenous procainamide (10 mg/kg body weight over a 5-minute period) or lidocaine (bolus of 50 mg) in β-blocker resistant sustained ventricular tachycardia. Cardiovert if hemodynamically unstable.

OTHER RHYTHM AND CONDUCTION DISTURBANCES

Supraventricular Arrhythmias

Incidence: Premature atrial complex 9.4% (range 1.2 to 27.8%). Supraventricular tachycardia 1.6% (range 0.0 to 7.0%). Atrial fibrillation 1.0% (range 0.3 to 2.2%). Complication specific publication (50).

Pathophysiology: Little is known about the mechanism of dobutamine stress in the induction of supraventricular arrhythmias. In one study (50), supraventricular arrhythmias occurred more frequently in patients with more extensive impairment of left ventricular function. The associated increase in left atrial size and pressure in such patients are well known predictors for these arrhythmias. In another study (8), supraventricular arrhythmias occurred more frequently in elderly patients.

Treatment: Discontinuation of dobutamine infusion (supraventricular arrhythmias are usually brief and self terminating). Intravenous β-blocker (metoprolol 5-10 mg, dose may be increased in case of existing high maintenance dose), verapamil (10 mg over 10 minutes, dose may be reduced in case of previous use of a beta-blocking drug or hypotension) or digoxine (bolus of 0.5 mg). Digoxin effects may take several hours and are therefore less useful for rapid rate control (61), but may be preferred in patients with left ventricular dysfunction. In regular supraventricular tachycardias, adenosine (intravenous bolus of 6 or 12 mg) may be helpful for diagnosis by induction of AV-block and may actually end circus movement tachycardias. Adenosine has a half-life of only 2 seconds so that adverse reactions (facial flushing, dyspnea) last only a short time (62). Cardiovert if hemodynamically unstable.

Atrioventricular Block

Incidence: 0.23% (range 0.03 to 0.68%). Complication specific publication (63).

Pathophysiology: Transient second or sometimes third degree AV-block may be induced by several mechanism such as myocardial ischemia (the conduction system is mainly supplied by the right coronary artery and more distally also by the left anterior descending artery), the Bezold-Jarisch reflex and latent abnormalities in the His-Purkinje system. In a detailed study of 12 patients with dobutamine stress-induced second degree AV-block by Hung *et al.* (63), the incidence of AV block was 4.0%, pointing to a higher incidence than that reported in the safety studies. All six patients with second degree AV-block Mobitz type II (usually located in the His bundle or bundle branches) had CAD (usually left anterior descending artery or two vessel CAD). In all but one patient AV-block occurred concomitantly with the onset of new wall motion abnormalities. After successful coronary revascularization AV block could not be induced by repeat DASE. In the six patients with second degree AV block Mobitz type I (Wenckebach block, usually located in the AV node) the relation with CAD and myocardial ischemia was less clear. Vagal mediated effects by the earlier described Bezold-Jarisch reflex (see section on asystole) could be a contributing factor is these patients. This assumption was supported by positive head-up tilt testing in all three patients with second degree AV-block Mobitz type I without CAD. AV-block is less common during this vagal reflex than sinus bradycardia, sinoatrial block or sinusarrest, probably because these sinus node problems protect the AV node. Finally, dobutamine enhances AV nodal conduction and may thus unravel latent abnormalities in the more distal His-Purkinje system.

Treatment: In Mobitz type II discontinuation of dobutamine infusion (of note, atropine may actually worsen subnodal block). In Mobitz type I (Wenckebach) block intravenous bolus of atropine (0.5 mg, may be repeated up to 2.0 mg) if necessary.

CORONARY SPASM

Incidence: True incidence unknown, 0.14% in one safety study (8). Case reports (46,64-71). Complication specific publication (72).

Pathophysiology: Coronary spasm during dobutamine stress is believed to result from α_1-receptor mediated coronary vasoconstriction (73), in particular in patients with endothelial dysfunction due to smoking, hypertension or diabetes (74,75). Systolic 'spasm' (or better compression) during dobutamine stress may be caused by myocardial bridging (71). In one study (72), including 51 patients with angina at rest accompanied with electrocardiographic ST-segment elevation, non-significant CAD and proven spasm (induced with acetylcholine), dobutamine stress provoked ST-segment elevation in 7 patients (14%). In another study (65), ST-segment elevation and wall motion abnormalities became evident only post dobutamine-stress after the administration of propranolol and it has been suggested that non-selective β-blockers may paradoxically exacerbate spasm by blocking the β_2- receptor mediated coronary vasodilatative effects of dobutamine. Alternatively, coronary spasm may be caused by hyperventilation in an anxious patient (76). Coronary spasm should be suspected in patients with dobutamine stress-induced ST-segment elevation in non-infarct leads and severe new wall motion abnormalities, although these may be absent in distal spasm (70), in combination with non-significant lesions at coronary angiography. ST-segment elevation in non-infarct leads has also been linked to transmural myocardial ischemia due to severe CAD (77-81). The final diagnosis of coronary spasm can only be confirmed at coronary angiography with ergonovine, acetylcholine, or dobutamine provocation (70,72).

Treatment: Sublingual nitroglycerin or nifedipine first rather than β-blocking agents (68,69) because of a small risk for exacerbation of spasm with a β-blocker (65). Long-term treatment with calcium-channel blockers. Risk factor modulation. Drug (cocaine) abstinence.

DISTURBANCES IN BLOOD PRESSURE

Hypotension

Incidence: As test endpoint 1.8% (range 0.2 to 7.6%). Dependent on definition, the overall incidence is much higher, a decrease >20 mm Hg is noticed in approximately 20% of patients (82,83). Complication specific publications (82-90).

Pathophysiology: Hypotension may result from an inadequate increase in cardiac output to compensate for an expected decrease in systemic vascular resistance, and/or a disproportionate decrease in systemic vascular resistance. An inadequate increase in cardiac output may be due to inadequate contractile reserve, severe ischemic left ventricular dysfunction, or fixed or dynamic left-sided obstructive heart disease. Dynamic left ventricular cavity obliteration due to strong inotropic stimulation was proposed as an important cause for reduced cardiac output and hypotension (87), but in later studies conflicting results have been reported for this mechanism as an important cause for hypotension (85,88-90). The second mechanism, a disproportionate decrease in systemic vascular resistance may be due to the earlier described Bezold-Jarisch reflex or rarely an allergic reaction to dobutamine (see later section on dobutamine hypersensitivity). The consistent absence of histories of prior MI or congestive heart failure (82,83), ischemia (16,82-86) or CAD (16,82,83,86) in studies with heterogeneous patients is indirect evidence of a dobutamine-induced hypotension mechanism that is primarily based on an excessive decrease in systemic vascular resistance, instead of a mechanism principally involving inadequate cardiac output in most patients. In patients with impaired left ventricular function (and thus a lesser role for the Bezold-Jarisch reflex) there is some evidence that contractile reserve plays a more important role in the pathogenesis of hypotension (59,91,92) and that hypotension has adverse prognostic value (91).

Treatment: Discontinue dobutamine infusion. Trendelenburg position. Rapid fluid infusion if symptomatic. In combination with sinus bradycardia exclude inferior wall ischemia and consider intravenous bolus of atropine (0.5-2 mg).

Hypertension

Incidence: As test endpoint 1.0% (range 0.2 to 3.5%). Complication specific publication 1.0% (93).

Pathophysiology: Stress-induced hypertension normally constitutes an end point for test termination because of safety concerns (94). Only two studies (11,93) analysed the clinical characteristics of patients with a marked hypertensive response. Such patients more often had a history of systemic hypertension, higher resting blood pressure and were more often on treatment with β-blockers compared to patients without a hypertensive response. These findings underscore the importance of adequate blood pressure control before dobutamine-atropine stress to avoid non-diagnostic tests. Alternatively, it was proposed (93) to earlier use atropine in patients with a marked hypertensive response because of only a mild additional effect on blood pressure and a marked chronotropic effect.

Treatment: Discontinue dobutamine infusion.

DIRECT SIDE-EFFECTS OF DOBUTAMINE-ATROPINE

Atropine Intoxication

Incidence: 0.03% (range 0.00 to 0.17%). No case reports.

Pathophysiology: Atropine intoxication is a central anticholinergic syndrome in which atropine acts on central nervous system cholinergic receptors causing altered mental status (confusion, delirium, hallucinations) or prolonged sedation for several hours. This syndrome is more

common in elderly patients and generally requires a dose of atropine of several milligrams (95).

Treatment: Physostigmine 1 to 2 mg intravenously can reverse the central atropine effects. Its administration also acts as a diagnostic test: rapid improvement rules out other causes of confusion such as cerebral stroke. Alternatively, it was proposed (96) to avoid atropine in the elderly and to give glycopyrrolate, a anticholinergic drug that does not cross the blood-brain barrier and so cannot cause a central anticholinergic syndrome.

Dobutamine Extravasation

Incidence: Only once reported in two patients in a safety study (5), but probably underreported. Case reports in continuous infusion (97,98).

Pathophysiology: Dobutamine accumulation in subcutaneous tissue can cause local vasoconstriction by stimulation of α_1-receptors which may result in limb ischemia (99) and during longer infusion even in necrosis (97). Dobutamine accumulation in subcutaneous tissue may also cause a local hypersensitivity reaction (see next section).

Treatment: Discontinuation of dobutamine infusion. Elevate involved extremity. Local injection of 5 to 10 mg phentolamine mesylate in 10 to 15 ml saline, a reversible, non-selective α-receptor antagonist.

Dobutamine Hypersensitivity

Incidence: Only three patients described in safety studies (6,15). Case reports, during continuous infusion, on local dermal lesions (100-102) and asthma (103).

Pathophysiology: Dobutamine solution contains sodium bisulfite that may cause allergic-type reactions with systemic symptoms and/or signs such as bronchospasm, flushing, tingling, pruritus, urticaria, angio-edema and hypotension or local dermal lesions characterized by

erythema, pruritus, cellulites and phlebitis with or without bullae formation at the side of the injection (104).

Treatment: Discontinuation of dobutamine infusion. Antihistamine therapy.

Discussion

Today's aggressive DASE protocol and expanding indications with inclusion of sicker patients have raised concerns about the safety of this stress modality (105). In the present meta-analysis, potentially life-threatening complications (cardiac rupture, acute MI, cerebrovascular accident, asystole, ventricular fibrillation and sustained ventricular tachycardia) occurred in 80 patients, of whom one died, accounting for one complication in approximately each 400 tests (Table 2).

Table 2. Incidence of Major Complications during 31,724 Dobutamine-Atropine Stress Echocardiographic Studies.

Complication	Number of Patients	Incidence Rate
Death	1	1 : 30 000
Cardiac rupture	1	1 : 30 000
Asystole	1	1 : 30 000
Cerebrovascular accident	3	1 : 10 000
Myocardial infarction	10	1 : 3 000
Ventricular fibrillation	13	1 : 2 500
Sustained ventricular tachycardia	51	1 : 600
Total major complications	80	1 : 400

It is important to notice that for exercise stress testing, dipyridamole stress echocardiography and dipyridamole stress scintigraphy lower complication rates were reported of one in approximately each 1100 (106), 1400 (107) and 1600 (108) tests, respectively. Several reasons may account for this difference. Patients referred for DASE are usually unable to exercise adequately and such patients are known to have a higher incidence and extent of CAD

(109,110). Also, the high-dose dobutamine-atropine stress protocol has a strong potential to induce myocardial ischemia. Exercise-induced ischemia may limit work load in a patient and this may prevent the development of severe ischemia during exercise stress. Pharmacological stress with the vasodilator dipyridamole primarily creates blood flow heterogeneity and true ischemia in only a limited number of patients with significant CAD (111). Finally, as described earlier, dobutamine may provoke ventricular arrhythmias by several unique mechanism. Indeed, the striking difference in complication rate is to a great extent caused by the high incidence rate of sustained ventricular tachycardia (and to a lesser extent also ventricular fibrillation) during dobutamine-atropine stress. When sustained ventricular tachycardia is excluded from our analysis, the complication rate is one complication in approximately each 1000 tests for dobutamine-atropine stress, each 1500 tests for exercise stress (106), and each 1700 test for both dipyridamole stress studies (107,108). Obviously, it is still essential to optimise the safety profile of DASE. This may be achieved by giving attention to patient selection, identification of patients at relative high-risk for complications, personnel issues and DASE protocol.

Patient selection. Safety starts with verification of test indication. Stress testing for diagnostic purposes is only useful in patients with an intermediate pre-test probability of CAD (112). In patients with a high pre-test probability of CAD there may be a case for prognostication but only then when DASE results really will affect patient management decisions. Subsequently, contraindications to DASE should be identified. Absolute contraindications include for dobutamine symptomatic severe aortic stenosis, acute aortic dissection, unstable coronary syndromes and hypertrophic cardiomyopathy and for atropine narrow-angle glaucoma, myasthenia gravis, and obstructive uropathy or gastrointestinal disorders. Relative contraindications include electrolyte abnormalities, intraventricular thrombus, intracranial or

abdominal aneurysm, known severe ventricular arrhythmias, high-degree AV-block and uncontrolled hypertension or atrial fibrillation. Although small DASE safety reports have been published in patients with a history of ventricular arrhythmias (113), left ventricular apical thrombus (114), intracranial aneurysms (36) and abdominal aneurysms (115), vasodilator stress testing seems intuitively the stress test of choice in such patients. After verification of indication and exclusion of contraindications, the procedure as well as side effects and potential complications should be explained to the patient. In patients at relative high-risk for complications (see next section) it may be good practice to obtain written informed consent by the patient. It should be noticed that in some countries dobutamine and atropine have even not been approved for pharmacological stress testing, making written informed consent by the patient necessary.

Identification of high-risk patients. Although severe complications can be sudden and unpredictable, clearly not each patient carries the same risk. All patients with cardiac rupture had a recent inferior MI, although it is controversial whether this particular myocardial region is relative susceptible for rupture (26,27). Ventricular fibrillation almost exclusively occurred in patients with impaired left ventricular function with induction of extensive myocardial ischemia. Identification of patients at relatively high-risk for acute MI may be more difficult. Although all but three patients had a history of CAD (usually prior MI), about half of the infarctions occurred in a myocardial territory without evidence for myocardial ischemia. This is consistent with the angiographic study by Ambrose *et al.* (116) in which the culprit vessel leading to acute MI had a mean initial stenosis of only 34%. Dobutamine-atropine stress will normally not induce myocardial ischemia in a myocardial territory supplied by a vessel with such a minor stenosis (117). As with other stress test, the relative risk of cardiac rupture, ventricular fibrillation or acute MI was four times higher in patients with a history of MI and/or

impaired left ventricular function. Therefore, the risk-benefit ratio of DASE in these patients should always be carefully evaluated.

Personnel. The current era of cost containment makes it challenging to dedicate physician time solely to the supervision of a time consuming test such as DASE. Paramedical supervision of exercise testing has been well established in the literature (118) and in selected patients this is allowed by the ACC/AHA Guidelines for Exercise Testing (119). Some have proposed to train nurse sonographers to fill the supervisory role during DASE (12). However, patients referred for DASE are usually not able to exercise adequately and therefore a priori at higher risk for induction of severe myocardial ischemia and complications. Furthermore, the experience with nurse sonographers to fill the supervisory role is sparse (5,12). Although some complications are largely independent of the operator's experience, there is a relation between the number of complications and the years of experience and volume of a centre (21). Therefore, we fully agree with Lattanzi *et al.* (105) that a physician with knowledge of the incidence, pathophysiology and treatment of complications should attend the test. In case of complications the physician should be able to prove that indications were appropriate, the protocol followed standard guidelines, the patient was aware of the inherent risks of the procedure, and that standard treatment was provided in a timely fashion.

DASE protocol. Controversy exists about the use (and definition) of stress-induced wall motion abnormalities as a test endpoint. This is clearly reflected in the 0% - 32% range in which this endpoint was used in the DASE safety studies. One may question whether continuation of DASE after the first clear signs of myocardial ischemia provides additional diagnostic or prognostic information and whether it is safe. There may be little loss of information when an examination is stopped because of signs of ischemia in one coronary

territory since the timing of ischemia (ischemic threshold) provides already excellent diagnostic (120) and prognostic (121) information. It is not known whether continuing DASE and potentially inducing ischemia in a multivessel distribution carries additional and independent information over the ischemic threshold. In patients with prior MI, ischemia outside the infarction territory may certainly be a test endpoint because this usually confirms multivessel CAD. Concerning the safety, it is important to note that provocation of severe myocardial ischemia played an important role in patients with ventricular fibrillation. The incidence of ventricular fibrillation was highest in studies with the most conservative use of this endpoint (17,47) and lowest in studies with the most liberal use of this endpoint (14,16).

It is well known that some life-threatening complications such as ventricular fibrillation (45), cerebrovascular accident (21) and in particular acute MI (4,5,11,21,28-31,60) can occur after dobutamine discontinuation, mostly within 20 minutes but up to 60 minutes has been described, despite its short half-life time and antidote administration. Thus, in particular in patients at risk for these complications, close cardiologic monitoring is required during the recovery phase and these patients should be instructed not to leave the hospital within one hour and immediately report any possible symptom of acute MI.

CONCLUSIONS

Potentially life-threatening complications during DASE occur in approximately one in each 400 studies. This relatively high complication rate is in particular driven by the occurrence of sustained ventricular tachycardia. Some of the important complications may occur within one hour after discontinuation of dobutamine infusion. Patients with a history of MI and/or impaired left ventricular function are at much higher risk for complications. The risk-benefit ratio of DASE should always be carefully evaluated.

References

1. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997;30:595-606.
2. McNeill AJ, Fioretti PM, el-Said SM, Salustri A, Forster T, Roelandt JR. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. Am J Cardiol 1992;70:41-46.
3. Mertes H, Sawada SG, Ryan T, Segar DS, Kovacs R, Foltz J, et al. Symptoms, adverse effects, and complications associated with dobutamine stress echocardiography. Experience in 1118 patients. Circulation 1993;88:15-19.
4. Picano E, Mathias W, Jr., Pingitore A, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. Echo Dobutamine International Cooperative Study Group. Lancet 1994;344:1190-1192.
5. Pellikka PA, Roger VL, Oh JK, Miller FA, Seward JB, Tajik AJ. Stress echocardiography. Part II. Dobutamine stress echocardiography: techniques, implementation, clinical applications, and correlations. Mayo Clin Proc 1995;70:16-27.
6. Zahn R, Lotter R, Nohl H, Schiele R, Bergmeier C, Zander M, et al. [Feasibility and safety of dobutamine stress echocardiography: experiences with 1,000 studies]. Z Kardiol 1996;85:28-34.
7. Hiro J, Hiro T, Reid CL, Ebrahimi R, Matsuzaki M, Gardin JM. Safety and results of dobutamine stress echocardiography in women versus men and in patients older and younger than 75 years of age. Am J Cardiol 1997;80:1014-1020.
8. Lamisse N, Cohen A, Chauvel C, Benhalima B, Desert I, Buyukoglu B, et al. [Dobutamine stress echocardiography; a monocentric experience on 600 consecutive patients. Effect of age]. Arch Mal Coeur Vaiss 1997;90:1455-1461.
9. Pinton R, Lemke W, Garcia LG. [Symptoms, complications and hemodynamic changes related to dobutamine stress echocardiography]. Arq Bras Cardiol 1997;69:161-164.
10. Hennessy TG, Codd MB, Kane G, McCarthy C, McCann HA, Sugrue DD. Safety of dobutamine stress echocardiography in 474 consecutive studies. Coron Artery Dis 1997;8:175-178.
11. Secknus MA, Marwick TH. Evolution of dobutamine echocardiography protocols and indications: safety and side effects in 3,011 studies over 5 years. J Am Coll Cardiol 1997;29:1234-1240.
12. Bremer ML, Monahan KH, Stussy VL, Miller FA, Jr., Seward JB, Pellikka PA. Safety of dobutamine stress echocardiography supervised by registered nurse sonographers. J Am Soc Echocardiogr 1998;11:601-605.
13. Pezzano A, Gentile F, Mantero A, Morabito A, Ravizza P. RITED (Registro Italiano Test Eco-Dobutamina): side effects and complications of echo-dobutamine stress test in 3041 examinations. G Ital Cardiol 1998;28:102-111.
14. Plonska E, Szwed H, Gasior Z, Drozdz J, Gackowski A, Szyszka A, et al. [Side effects during dobutamine stress echocardiography: analysis of 582 studies]. Pol Merkuriusz Lek 1999;7:164-168.
15. Mathias W, Jr., Arruda A, Santos FC, Arruda AL, Mattos E, Osorio A, et al. Safety of dobutamine-atropine stress echocardiography: A prospective experience of 4,033 consecutive studies. J Am Soc Echocardiogr 1999;12:785-791.

16. Takeuchi M, Miura Y, Sonoda S, Kuroiwa A. Comparison of Three Different Protocols for Dobutamine Stress Echocardiography: Does the Addition of Atropine Increase Complications, and Does It Improve Diagnostic Accuracy? Echocardiography 1999;16:347-355.
17. Poldermans D, Fioretti PM, Boersma E, Bax JJ, Thomson IR, Roelandt JR, et al. Long-term prognostic value of dobutamine-atropine stress echocardiography in 1737 patients with known or suspected coronary artery disease: A single-center experience. Circulation 1999;99:757-762.
18. Chenzbraun A, Khoury Z, Gottlieb S, Keren A. Impact of Age on the Safety and the Hemodynamic Response Pattern During High Dose Dobutamine Echocardiography. Echocardiography 1999;16:135-142.
19. Hirano Y, Yamamoto T, Uehara H, Nakamura H, Wufuer M, Yamada S, et al. [Complications of stress echocardiography]. J Cardiol 2001;38:73-80.
20. Cortigiani L, Picano E, Coletta C, Chiarella F, Mathias W, Gandolfo N, et al. Safety, feasibility, and prognostic implications of pharmacologic stress echocardiography in 1482 patients evaluated in an ambulatory setting. Am Heart J 2001;141:621-629.
21. Rodriguez Garcia MA, Iglesias-Garriz I, Corral Fernandez F, Garrote Coloma C, Alonso-Orcajo N, Branco L, et al. [Evaluation of the safety of stress echocardiography in Spain and Portugal]. Rev Esp Cardiol 2001;54:941-948.
22. Reisenhofer B, Squarcini G, Picano E. Cardiac rupture during dobutamine stress test. Ann Intern Med 1998;128:605.
23. Orlandini AD, Tuero EI, Diaz R, Vilamajo OA, Paolasso EA. Acute cardiac rupture during dobutamine-atropine echocardiography stress test. J Am Soc Echocardiogr 2000;13:152-153.
24. Zamorano J, Moreno R, Almeria C, Serra V, Rodrigo J, Sanchez-Harguindey L. [Left ventricular free wall rupture during dobutamine stress echocardiography]. Rev Esp Cardiol 2002;55:312-314.
25. Daniels CJ, Orsinelli DA. Cardiac rupture with dobutamine stress echocardiography. J Am Soc Echocardiogr 1997;10:979-981.
26. Oliva PB, Hammill SC, Edwards WD. Cardiac rupture, a clinically predictable complication of acute myocardial infarction: report of 70 cases with clinicopathologic correlations. J Am Coll Cardiol 1993;22:720-726.
27. Slater J, Brown RJ, Antonelli TA, Menon V, Boland J, Col J, et al. Cardiogenic shock due to cardiac free-wall rupture or tamponade after acute myocardial infarction: a report from the SHOCK Trial Registry. Should we emergently revascularize occluded coronaries for cardiogenic shock? J Am Coll Cardiol 2000;36:1117-1122.
28. Lewis WR, Arena FJ, Galloway MT, Bommer WJ. Acute myocardial infarction associated with dobutamine stress echocardiography. J Am Soc Echocardiogr 1997;10:576-578.
29. Takeuchi M, Sonoda S, Hanada H, Numata T, Nakashima Y. Acute myocardial infarction in a patient during dobutamine stress echocardiography. Cathet Cardiovasc Diagn 1997;41:404-406.
30. Weidmann B, Lepique CU, Jansen W, Stoiber WU, Tauchert MO. Myocardial infarction as a complication of dobutamine stress echocardiography. J Am Soc Echocardiogr 1997;10:768-771.
31. Pressman GS. Acute infarction of a previously stented coronary artery precipitated by dobutamine stress echocardiography. J Am Soc Echocardiogr 2000;13:150-151.
32. Ferreira AC, de Marchena E, Mayor M, Bolooki H. Sinus of Valsalva aneurysm presenting as myocardial infarction during dobutamine stress test. Cathet Cardiovasc Diagn 1996;39:400-402.

33. Breithardt OA, Flachskampf FA, Klues HG. [Life threatening acute complications of dobutamine-atropine stress echocardiography--a case report]. Z Kardiol 1998;87:492-498.
34. Galloway MT, Paglieroni TG, Wun T, Arena FJ, Lewis WR. Platelet activation during dobutamine stress echocardiography. Am Heart J 1998;135:888-900.
35. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2003;24:28-66.
36. Takhtehchian DS, Novaro GM, Barnett G, Griffin BP, Pellikka PA. Safety of dobutamine stress echocardiography in patients with unruptured intracranial aneurysms. J Am Soc Echocardiogr 2002;15:1401-1404.
37. Hacke W, Kaste M, Skyhoj Olsen T, Orgogozo JM, Bogousslavsky J. European Stroke Initiative (EUSI) recommendations for stroke management. The European Stroke Initiative Writing Committee. Eur J Neurol 2000;7:607-623.
38. Lanzarini L, Previtali M, Diotallevi P. Syncope caused by cardiac asystole during dobutamine stress echocardiography. Heart 1996;75:320-321.
39. Salustri A, Biferali F, Palamara A. Cardiac arrest during dobutamine stress echocardiography. G Ital Cardiol 1997;27:69-71.
40. Pinton R, Haggi Filho H, Lemke W, Franca Neto OR. [Cardiac asystole during dobutamine stress echocardiography]. Arq Bras Cardiol 1998;70:435-436.
41. Hopfenspirger MR, Miller TD, Christian TF, Gibbons RJ. Sinus node deceleration during dobutamine perfusion scintigraphy as a marker of inferior ischemia. Am J Cardiol 1994;74:817-819.
42. Mark AL. The Bezold-Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. J Am Coll Cardiol 1983;1:90-102.
43. Waxman MB, Asta JA, Cameron DA. Vasodepressor reaction induced by inferior vena cava occlusion and isoproterenol in the rat. Role of beta 1- and beta 2-adrenergic receptors. Circulation 1994;89:2401-2411.
44. Pontillo D, Capezzuto A. Dobutamine, dipyridamole, and stress echocardiography. Circulation 1996;93:617.
45. Varga A, Picano E, Lakatos F. Fatal ventricular fibrillation during a low-dose dobutamine stress test. Am J Med 2000;108:352-353.
46. Shaheen J, Mendzelevski B, Tzivoni D. Dobutamine-induced ST segment elevation and ventricular fibrillation with nonsignificant coronary artery disease. Am Heart J 1996;132:1058-1060.
47. Poldermans D, Fioretti PM, Boersma E, Forster T, van Urk H, Cornel JH, et al. Safety of dobutamine-atropine stress echocardiography in patients with suspected or proven coronary artery disease. Am J Cardiol 1994;73:456-459.
48. De Sutter J, Poldermans D, Vourvouri E, Van Donburg R, Elhendy A, Bax J, et al. Long-term prognostic significance of complex ventricular arrhythmias induced during dobutamine stress echocardiography. Am J Cardiol 2003;91:242-244.
49. Bigi R, Partesana N, Verzoni A, Bandini P, Maffi M, Longoni A, et al. Incidence and correlates of complex ventricular arrhythmias during dobutamine stress echocardiography after acute myocardial infarction. Eur Heart J 1995;16:1819-1824.
50. Elhendy A, van Domburg RT, Bax JJ, Roelandt JR. Relation between the extent of coronary artery disease and tachyarrhythmias during dobutamine stress echocardiography. Am J Cardiol 1999;83:832-835.
51. Madu EC, Price A, Harris T, Badran H, Rouse C, Ramanathan KB. Sustained nonischemic ventricular tachycardia during dobutamine stress echocardiography.

Cardiology 1996;87:82-85.
52. Poldermans D, ten Cate FJ, Elhendy A, Rocchi G, Bax JJ, Vletter W, et al. Ventricular tachycardia during dobutamine stress myocardial contrast imaging. Chest 1999;115:307-308.
53. Previtali M, Lanzarini L, Fetiveau R, Poli A, Diotallevi P. Dobutamine-induced and spontaneous sustained ventricular tachycardia in recent myocardial infarction. Eur Heart J 1996;17:803-804.
54. John RM, Taggart PI, Sutton PM, Ell PJ, Swanton H. Direct effect of dobutamine on action potential duration in ischemic compared with normal areas in the human ventricle. J Am Coll Cardiol 1992;20:896-903.
55. O'Sullivan CA, Henein MY, Sutton R, Coats AJ, Sutton GC, Gibson DG. Abnormal ventricular activation and repolarisation during dobutamine stress echocardiography in coronary artery disease. Heart 1998;79:468-473.
56. Brodde OE, O'Hara N, Zerkowski HR, Rohm N. Human cardiac beta-adrenoceptors: both beta 1- and beta 2-adrenoceptors are functionally coupled to the adenylate cyclase in right atrium. J Cardiovasc Pharmacol 1984;6:1184-1191.
57. Priori SG, Corr PB. Mechanisms underlying early and delayed afterdepolarizations induced by catecholamines. Am J Physiol 1990;258:H1796-805.
58. Coma-Canella I. Changes in plasma potassium during the dobutamine stress test. Int J Cardiol 1991;33:55-59.
59. Cornel JH, Balk AH, Boersma E, Maat AP, Elhendy A, Arnese M, et al. Safety and feasibility of dobutamine-atropine stress echocardiography in patients with ischemic left ventricular dysfunction. J Am Soc Echocardiogr 1996;9:27-32.
60. Mathias Junior W, Beneti LP, dos Santos FC, Duprat R, Beraldo A, Gil MA, et al. [Safety and feasibility of dobutamine-atropine stress echocardiography]. Arq Bras Cardiol 1997;69:31-34.
61. Schreck DM, Rivera AR, Tricarico VJ. Emergency management of atrial fibrillation and flutter: intravenous diltiazem versus intravenous digoxin. Ann Emerg Med 1997;29:135-140.
62. Lerman BB, Belardinelli L. Cardiac electrophysiology of adenosine. Basic and clinical concepts. Circulation 1991;83:1499-1509.
63. Hung KC, Lin FC, Chern MS, Chang HJ, Hsieh IC, Wu D. Mechanisms and clinical significance of transient atrioventricular block during dobutamine stress echocardiography. J Am Coll Cardiol 1999;34:998-1004.
64. Varga A, Cortigiani L, Rossi PC, Cseh E, De Nes M, Trivieri MG, et al. Coronary vasospasm as a source of false positive results during dobutamine echocardiography. Cardiologia 1999;44:907-912.
65. Alvarez L, Zamorano J, Mataix L, Almeria C, Moreno R, Rodrigo JL. [Coronary Spasm after Administration of Propranolol during Dobutamine Stress Echocardiography]. Rev Esp Cardiol 2002;55:778-781.
66. Deligonul U, Armbruster R, Hailu A. Provocation of coronary spasm by dobutamine stress echocardiography in a patient with angiographically minimal coronary artery disease. Clin Cardiol 1996;19:755-758.
67. Roffi M, Meier B, Allemann Y. Angiographic documented coronary arterial spasm in absence of critical coronary artery stenoses in a patient with variant angina episodes during exercise and dobutamine stress echocardiography. Heart 2000;83:E4.
68. Cohen A, Chauvel C, Benhalima B, Blanchard B. Complication of dobutamine stress echocardiography. Lancet 1995;345:201-202.
69. Mathew J, Thannoli N, Narra L, el Khadra M. Transmural myocardial ischaemia during dobutamine stress echocardiography. Lancet 1995;346:383-384.

70. Yamagishi H, Watanabe H, Toda I, Yoshiyama M, Akioka K, Teragaki M, et al. A case of dobutamine-induced coronary arterial spasm with ST-segment elevation. Jpn Circ J 1998;62:150-151.
71. Tio RA, Van Gelder IC, Boonstra PW, Crijns HJ. Myocardial bridging in a survivor of sudden cardiac near-death: role of intracoronary doppler flow measurements and angiography during dobutamine stress in the clinical evaluation. Heart 1997;77:280-282.
72. Kawano H, Fujii H, Motoyama T, Kugiyama K, Ogawa H, Yasue H. Myocardial ischemia due to coronary artery spasm during dobutamine stress echocardiography. Am J Cardiol 2000;85:26-30.
73. Dai XZ, Chen DG, Bache RJ. Alpha-adrenergic effects of dopamine and dobutamine on the coronary circulation. J Cardiovasc Pharmacol 1989;14:82-87.
74. Caralis DG, Deligonul U, Kern MJ, Cohen JD. Smoking is a risk factor for coronary spasm in young women. Circulation 1992;85:905-909.
75. Vita JA, Treasure CB, Nabel EG, McLenachan JM, Fish RD, Yeung AC, et al. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. Circulation 1990;81:491-497.
76. Previtali M, Ardissino D, Barberis P, Panciroli C, Chimienti M, Salerno JA. Hyperventilation and ergonovine tests in Prinzmetal's variant angina pectoris in men. Am J Cardiol 1989;63:17-20.
77. Kamalesh M, Chandrasekaran K, Sivaram CA, Thadani U. Lack of arrhythmogenicity with ST-segment elevation during high-dose of dobutamine atropine stress in patients with documented or suspected coronary artery disease. Am J Cardiol 1997;80:341-343.
78. Elhendy A, Cornel JH, Roelandt JR, van Domburg RT, Geleijnse MI, Nierop PR, et al. Relation between ST segment elevation during dobutamine stress test and myocardial viability after a recent myocardial infarction. Heart 1997;77:115-121.
79. Coma-Canella I. Dobutamine stress test to diagnose the presence and severity of coronary artery lesions in angina. Eur Heart J 1991;12:1198-1204.
80. Previtali M, Lanzarini L, Mussini A, Ferrario M, Angoli L, Specchia G. Dobutamine-induced ST segment elevation in a patient with angina at rest and critical coronary lesions. Eur Heart J 1992;13:997-999.
81. Previtali M, Fetiveau R, Lanzarini L, Cavalotti C. Dobutamine-induced ST-segment elevation in patients without myocardial infarction. Am J Cardiol 1998;82:1528-1530, A7.
82. Marcovitz PA, Bach DS, Mathias W, Shayna V, Armstrong WF. Paradoxic hypotension during dobutamine stress echocardiography: clinical and diagnostic implications. J Am Coll Cardiol 1993;21:1080-1086.
83. Geleijnse ML, Elhendy A, van Domburg RT, Rambaldi R, Reijs AE, Roelandt JR, et al. Prognostic significance of systolic blood pressure changes during dobutamine-atropine stress technetium-99m sestamibi perfusion scintigraphy in patients with chest pain and known or suspected coronary artery disease. Am J Cardiol 1997;79:1031-1035.
84. Lieberman EB, Heinle SK, Wildermann N, Waugh RA, Kisslo JA, Bashore TM. Does hypotension during dobutamine stress echocardiography correlate with anatomic or functional cardiac impairment? Am Heart J 1995;129:1121-1126.
85. Heinle SK, Tice FD, Kisslo J. Hypotension during dobutamine stress echocardiography: is it related to dynamic intraventricular obstruction? Am Heart J 1995;130:314-317.
86. Rallidis LS, Moyssakis IE, Nihoyannopoulos P. Hypotensive response during dobutamine stress echocardiography in coronary patients: a common event of well-

functioning left ventricle. Clin Cardiol 1998;21:747-752.
87. Pellikka PA, Oh JK, Bailey KR, Nichols BA, Monahan KH, Tajik AJ. Dynamic intraventricular obstruction during dobutamine stress echocardiography. A new observation. Circulation 1992;86:1429-1432.
88. Khanal S, Daggubati R, Gaalla A, Shah PM, Pai RG. Left ventricular cavity obliteration during dobutamine stress echocardiography is associated with female sex and left ventricular size and function. J Am Soc Echocardiogr 1998;11:957-960.
89. Luria D, Klutstein MW, Rosenmann D, Shaheen J, Sergey S, Tzivoni D. Prevalence and significance of left ventricular outflow gradient during dobutamine echocardiography. Eur Heart J 1999;20:386-392.
90. Sorrentino MJ, Marcus RH, Lang RM. Left ventricular outflow tract obstruction as a cause for hypotension and symptoms during dobutamine stress echocardiography. Clin Cardiol 1996;19:225-230.
91. Wang CH, Cherng WJ, Hung MJ. Dobutamine-induced hypotension is an independent predictor for mortality in patients with left ventricular dysfunction following myocardial infarction. Int J Cardiol 1999;68:297-302.
92. Elhendy A, van Domburg RT, Nierop PR, Geleijnse ML, Bax JJ, Kasprzak JD, et al. Impaired systolic blood pressure response to dobutamine stress testing: a marker of more severe functional abnormalities in patients with myocardial infarction. J Am Soc Echocardiogr 1998;11:436-441.
93. Lee CY, Pellikka PA, Shub C, Sinak LJ, Seward JB. Hypertensive response during dobutamine stress echocardiography. Am J Cardiol 1997;80:970-971.
94. Cayen B, Cullen N. Intracerebral haemorrhage in previously healthy adults following aerobic and anaerobic exercise. Brain Inj 2002;16:397-405.
95. Pestalozzi BC, Caduff F. [Group poisoning by belladonna]. Schweiz Med Wochenschr 1986;116:924-926.
96. Myles P. Dobutamine-atropine stress echocardiography and central anticholinergic syndrome. Lancet 1994;344:1636.
97. Hoff JV, Peatty PA, Wade JL. Dermal necrosis from dobutamine. N Engl J Med 1979;300:1280.
98. Leier CV, Webel J, Bush CA. The cardiovascular effects of the continuous infusion of dobutamine in patients with severe cardiac failure. Circulation 1977;56:468-472.
99. MacCara ME. Extravasation: a hazard of intravenous therapy. Drug Intell Clin Pharm 1983;17:713-717.
100. Wu CC, Chen WJ, Cheng JJ, Hsieh YY, Lien WP. Local dermal hypersensitivity from dobutamine hydrochloride (Dobutrex solution) injection. Chest 1991;99:1547-1548.
101. McCauley CS, Blumenthal MS. Dobutamine and pruritus of the scalp. Ann Intern Med 1986;105:966.
102. Cernek PK. Dermal cellulitis--a hypersensitivity reaction from dobutamine hydrochloride. Ann Pharmacother 1994;28:964.
103. Epailly E, Blaumeiser M, Gonzales M, Cantineau A. [Suspicion of asthma due to dobutamine chlorhydrate. Apropos of a case]. Therapie 1994;49:52-53.
104. Smolinske SC. Review of parenteral sulfite reactions. J Toxicol Clin Toxicol 1992;30:597-606.
105. Lattanzi F, Picano E, Adamo E, Varga A. Dobutamine stress echocardiography: safety in diagnosing coronary artery disease. Drug Saf 2000;22:251-262.
106. Stuart RJ, Jr., Ellestad MH. National survey of exercise stress testing facilities. Chest 1980;77:94-97.
107. Picano E, Marini C, Pirelli S, Maffei S, Bolognese L, Chiriatti G, et al. Safety of intravenous high-dose dipyridamole echocardiography. The Echo-Persantine

International Cooperative Study Group. Am J Cardiol 1992;70:252-258.
108. Lette J, Tatum JL, Fraser S, Miller DD, Waters DD, Heller G, et al. Safety of dipyridamole testing in 73,806 patients: the Multicenter Dipyridamole Safety Study. J Nucl Cardiol 1995;2:3-17.
109. Deckers JW, Fioretti P, Brower RW, Simoons ML, Baardman T, Hugenholtz PG. Ineligibility for predischarge exercise testing after myocardial infarction in the elderly: implications for prognosis. Eur Heart J 1984;5 Suppl E:97-100.
110. Froelicher VF, Perdue S, Pewen W, Risch M. Application of meta-analysis using an electronic spread sheet to exercise testing in patients after myocardial infarction. Am J Med 1987;83:1045-1054.
111. Fung AY, Gallagher KP, Buda AJ. The physiologic basis of dobutamine as compared with dipyridamole stress interventions in the assessment of critical coronary stenosis. Circulation 1987;76:943-951.
112. Geleijnse ML, Marwick TH, Boersma E, Deckers JW, Melin JA, Fioretti PM. Optimal pharmacological stress testing for the diagnosis of coronary artery disease: a probabilistic approach. Eur Heart J 1995;16 Suppl M:3-10.
113. Elhendy A, Windle J, Porter TR. Safety and feasibility of dobutamine stress echocardiography in patients with implantable cardioverter defibrillators. Am J Cardiol 2003;92:475-477.
114. Cusick DA, Bonow RO, Chaudhry FA. Safety of dobutamine stress echocardiography in patients with left ventricular apical thrombus. Am J Cardiol 1997;80:1252-1254.
115. Pellikka PA, Roger VL, Oh JK, Seward JB, Tajik AJ. Safety of performing dobutamine stress echocardiography in patients with abdominal aortic aneurysm > or = 4 cm in diameter. Am J Cardiol 1996;77:413-416.
116. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56-62.
117. Baptista J, Arnese M, Roelandt JR, Fioretti P, Keane D, Escaned J, et al. Quantitative coronary angiography in the estimation of the functional significance of coronary stenosis: correlations with dobutamine- atropine stress test. J Am Coll Cardiol 1994;23:1434-1439.
118. Franklin BA, Gordon S, Timmis GC, O'Neill WW. Is direct physician supervision of exercise stress testing routinely necessary? Chest 1997;111:262-265.
119. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, et al. ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997;30:260-311.
120. Panza JA, Curiel RV, Laurienzo JM, Quyyumi AA, Dilsizian V. Relation between ischemic threshold measured during dobutamine stress echocardiography and known indices of poor prognosis in patients with coronary artery disease. Circulation 1995;92:2095-2101.
121. Poldermans D, Arnese M, Fioretti PM, Salustri A, Boersma E, Thomson IR, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. J Am Coll Cardiol 1995;26:648-653.

CHAPTER 4

Adverse Reactions After the Use of Sulphur Hexafluoride (Sonovue®) Echo Contrast Agent

submitted

Marcel L. Geleijnse

Wim B. Vletter

Attila Nemes

Michelle Michels

Osama I.I. Soliman

Kadir Caliskan

Tjebbe W. Galema

Folkert J. ten Cate

Abstract

Objective. To study the adverse effects of SonoVue® echo contrast in a consecutive series of cardiac patients.

Design. During a 4-year period all adverse effects of SonoVue® contrast agent applied for diagnostic cardiac echocardiographic studies were noted.

Setting. Tertiary referral center.

Patients. Consecutive patients referred for a diagnostic SonoVue® contrast cardiac echocardiographic study.

Results. During 352 consecutive cardiac SonoVue® studies, seven patients (2.0%) experienced adverse effects. Four patients (1.1%) had mild allergic reactions causing skin erythema and mild sinus tachycardia, three patients (0.9%) experienced a severe allergic reaction resulting in (non-fatal) anaphylactic shock.

Conclusions. The reported incidence of adverse effects of SonoVue® echo contrast in this consecutive series of cardiac patients seems markedly higher than those reported in a company post-marketing analysis and await confirmation.

SonoVue® (Bracco, Milan, Italy) is a blood pool ultrasound contrast agent based on microbubbles stabilised by a phospholipids shell and filled with sulphur hexafluoride gas (1,2). It is isotonic to human plasma and claimed to be devoid of antigenic potential, as it does not contain any proteineous material. SonoVue® has been approved in Europe and other countries for the improvement in endocardial border delineation during echocardiography and other, non-cardiac applications. However, throughout Europe a number of serious allergic reactions with probable secondary cardiovascular problems have been reported to national and international registry authorities (3,4). Three of these reports included even fatal outcome soon after the administration of SonoVue® in patients with severe coronary artery disease. Despite questions about the causal relationship, the European Medicines Agency (EMEA) recently took precautionary measures to limit the use of SonoVue® in patients with cardiac disease (www.emea.eu.int/humandocs/Humans/EPAR/ SonoVue/SonoVue.htm). As a result of the EMEA interventions, SonoVue® is contra-indicated in cardiac patients with an (suspected) acute coronary syndrome, recent percutaneous coronary intervention, acute or chronic severe (NYHA class III/IV) heart failure or severe cardiac arrhythmias. In our cardiac department we have been using SonoVue® since mid 2001. Because of safety concerns we systematically reviewed in a consecutive series of patients all adverse effects of SonoVue® in our echocardiographic laboratory.

Mild adverse reactions

During a 4-year period 352 SonoVue® echo contrast studies were performed in 274 patients for a variety of reasons (5,6). One hundred and ninety-eight patients underwent only one SonoVue® study, whereas 77 patients underwent multiple SonoVue® studies. Mild adverse reactions, including skin erythema and mild sinus tachycardia, were seen in four patients (1.1%). These mild reactions were present in 2 out of the 198 patients (1.0%) who received

SonoVue® only once and 2 out of the 76 patients (2.6%) who received SonoVue® twice. All four patients were successfully treated with intravenous clemastine and hydrocortisone.

Severe adverse reactions

During the same 4-year period an additional three patients (0.9%), who all underwent SonoVue® echocardiography for the first time, experienced a severe anaphylactic reaction.

Case 1 (August 21, 2001)

An 80-year-old man known with hypertension and recent (3 weeks earlier) carotid stenting was referred to dobutamine stress echocardiography for risk stratification before aortic abdominal surgery. Medical treatment included acetyl salicylic acid, clopidogrel, calcium antagonist, beta-blocker and diuretics. The patient did not experience angina during exercise nor were there symptoms of heart failure. Because of poor quality of the echo window, SonoVue® contrast was used. During recording of the resting echo images (with 0.75 ml SonoVue®) the patient developed extensive skin erythema and anaphylactic shock with a decrease in blood pressure from 150/70 to 70/30 mmHg. Clemastine 2 mg and hydrocortisone 100 mg were immediately injected intravenously and volume resuscitation (300 ml gelofusine) was applied. After 10 minutes, the patient fully recovered and the blood pressure returned to a normal level (145/80 mmHg). After a night observation in the clinical department he was discharged the next day. Dobutamine stress technetium-99m SPECT, performed at the outpatient clinic, did not show reversible perfusion defects and the patient was cleared for vascular surgery.

Case 2 (February 24, 2005)

A 68-year-old woman known with Pompe's disease (a lysosomal glycogen storage disease due to α-glucosidase deficiency) was referred for SonoVue® contrast echocardiography because of

an ongoing study protocol to investigate cardiac function in these patients. Left ventricular end-diastolic diameter was 46 mm and ejection fraction was 83%. Due to Pompe's disease the patient was in a poor clinical condition with a severely limited exercise tolerance and need for intermittent use of a respirator machine. After bolus injection of 0.5 ml and two repeat injections of 0.25 ml of SonoVue® the patient experienced tinnitus and dizziness. Blood pressure decreased from 140/80 to 70/40 mm Hg and sinus rate decreased from 90 to 50 beats per minute after which the patient became subconscious. Clemastine 2 mg and hydrocortisone 100 mg were immediately injected intravenously and volume resuscitation (150 ml gelofusine) was applied. After 15 minutes the patient completely recovered and returned to the neurological department.

Case 3 (September 15, 2005)

A 34-year-old man known with familiar non-ischemic dilated cardiomyopathy was referred for SonoVue® contrast echocardiography to exclude non-compaction cardiomyopathy (5). Left ventricular end-diastolic diameter was 69 mm and ejection fraction was 37%. The patient was in stable NYHA heart failure class I-II for years without evidence for high filling pressures. Medical treatment included ACE inhibition, beta-blocker and diuretics. After bolus injection of 0.5 ml and an additional 0.25 ml of SonoVue® the patient experienced a heat sensation with nausea and extensive skin erythema after which sinus bradycardia developed. Despite immediate intravenous injection of clemastine 2 mg and hydrocortisone 100 mg the patient went into anaphylactic shock with extreme brady-arrhythmia (<30 beats per minute), lost conscious and started gasping. After a short-lasting resuscitation procedure (cardiac massage and manual ventilation) of approximately three minutes the patient fully recovered. The patient was observed in the clinical department from which he was discharged the same day. Ten hours after discharge, the patient experienced pain in multiple joints lasting for two days.

Immunological analysis revealed a type III allergic reaction without identification of a specific allergen.

Clinical implications

Throughout Europe a number of serious allergic reactions with probable secondary cardiovascular problems have been reported to national and international registry authorities (3,4). These allergic reactions may be caused by the SonoVue® sulphur hexafluoride gas or the shell component polyethylene glycol (macrogol 4000) (7-9). In a Bracco company post-marketing analysis in 157,838 patients, 19 non-fatal severe (0.01%) and 3 fatal (0.002%) complications after the use of SonoVue® were reported. Obviously, the risks and benefits of SonoVue® should be weighted and these should be compared with other diagnostic tests. Unfortunately, clinical outcome studies for SonoVue® are not yet published. So, this leaves us with two basic questions. What is the risk of SonoVue® and how does this risk compare with other diagnostic modalities? The complication rates in the registry are, although somewhat higher compared to Optison® (4), not higher than the complication rates of intravascular contrast media used in radiology (10,11). This is an important finding because patients referred for a cardiac study are in general at a higher risk to develop secondary cardiovascular problems. We should, however, realize that it is difficult for a post-marketing analysis to define a test as low-risk because of potential underreporting of complications. Therefore, it is essential that consecutive series of patients should be prospectively monitored for complications in institutions. In our study population of 352 consecutive cardiac studies, seven patients (2.0%) experienced adverse effects, including anaphylactic shock in three patients (0.9%). These numbers seem higher than those reported in the registry and await confirmation. For this moment, we strongly emphasize the EMEA guideline that it is recommended to keep the patient under close medical supervision during and for at least 30 minutes following the

administration of SonoVue®. Intravenous anti-allergic and anaphylactic drugs (H1 and H2-antihistamines, corticosteroids and epinephrine) should be available in the echo room in addition to standard resuscitation equipment (12). Apart from the existing contra-indications caution is advised in all patients, and in particular those patients with a compromised cardio-pulmonary status.

References

1. Schneider M, Arditi M, Barrau MB, Brochot J, Broillet A, Ventrone R, et al. BR1: a new ultrasonographic contrast agent based on sulfur hexafluoride-filled microbubbles. Invest Radiol 1995;30:451-457.

2. Schneider M. Characteristics of SonoVuetrade mark. Echocardiography 1999;16:743-746.

3. de Groot MC, van Zwieten-Boot BJ, van Grootheest AC. [Severe adverse reactions after the use of sulphur hexafluoride (SonoVue) as an ultrasonographic contrast agent]. Ned Tijdschr Geneeskd 2004;148:1887-1888.

4. Dijkmans PA, Visser CA, Kamp O. Adverse reactions to ultrasound contrast agents: is the risk worth the benefit? Eur J Echocardiogr 2005;6:363-366.

5. de Groot-de Laat LE, Krenning BJ, ten Cate FJ, Roelandt JR. Usefulness of contrast echocardiography for diagnosis of left ventricular noncompaction. Am J Cardiol 2005;95:1131-1134.

6. Biagini E, Galema TW, Schinkel AF, Vletter WB, Roelandt JR, Ten Cate FJ. Myocardial wall thickness predicts recovery of contractile function after primary coronary intervention for acute myocardial infarction. J Am Coll Cardiol 2004;43:1489-1493.

7. Pirila V. Skin allergy to simple gaseous sulphur compounds. Acta Allergol 1954;7:387-402.

8. Fisher AA. Immediate and delayed allergic contact reactions to polyethylene glycol. Contact Dermatitis 1978;4:135-138.

9. Dewachter P, Mouton-Faivre C. Anaphylaxis to macrogol 4000 after a parenteral corticoid injection. Allergy 2005;60:705-706.

10. Shehadi WH, Toniolo G. Adverse reactions to contrast media: a report from the Committee on Safety of Contrast Media of the International Society of Radiology. Radiology 1980;137:299-302.

11. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990;175:621-628.

12. Ellis AK, Day JH. Diagnosis and management of anaphylaxis. Cmaj 2003;169:307-311.

CHAPTER 5

Current Status of Real-Time Three-Dimensional Stress Echocardiography

submitted

Attila Nemes

Marcel L. Geleijnse

Johan G. Bosch

Osama I.I. Soliman

Ashraf M. Anwar

Boudewijn J. Krenning

Wim B. Vletter

Folkert J. ten Cate

Abstract

Two-dimensional stress echocardiography is a non-invasive imaging stress modality with a continuously evolving spectrum of indications. Although the diagnostic and prognostic roles of stress echocardiography are well established, it is widely known that stress echocardiography suffers from a number of limitations. Real-time three-dimensional echocardiography has been advocated to solve some of these problems. The aim of the present state-of-the-art paper is to discuss the benefits and current limitations of this new stress methodology.

Introduction

Two-dimensional (2D) stress echocardiography is a non-invasive stress modality with a continuously evolving spectrum of indications. One of the most important indications is the identification of patients with coronary artery disease (1). For this purpose, wall motion of left ventricular (LV) segments is compared between rest, low-dose, and peak stress on several standardized LV views. The rationale for the use of 2D stress echocardiography is that cardiovascular stress will in the presence of significant coronary disease result in myocardial ischemia, manifested as a regional wall motion abnormality. Although the diagnostic and prognostic roles of 2D stress echocardiography are well established (1, 2), it is widely known that stress echocardiography suffers from a number of limitations. Suboptimal diagnostic accuracy may be caused by inadequate image quality, comparisons of non-identical LV wall segments at rest, low-dose, and peak stress, and smaller ischemic areas may be missed in the limited available LV cross sections. Also, interpretation of 2D stress echocardiography is subjective with different existing definitions of abnormality and considerable inter-observer and inter-institutional diagnostic variability (3). Three-dimensional (3D) stress echocardiography has been advocated to improve the suboptimal diagnostic accuracy.

ACQUISITION AND ANALYSIS OF 3D IMAGES

From one single apical window the full LV volume data set can be acquired. This process may be facilitated by use of two displayed reference 2D images, such as an apical four-chamber and an orthogonal view. Full LV volume is acquired by scanning of four subvolumes of ~20° x 80° during four (Philips iE33) or seven (Philips Sonos 7500) consecutive, electrocardiographically triggered, heartbeats. These LV subvolumes are automatically integrated by the system into one pyramidal data set of ~80° x 80°, incorporating full LV volume (Figure 1).

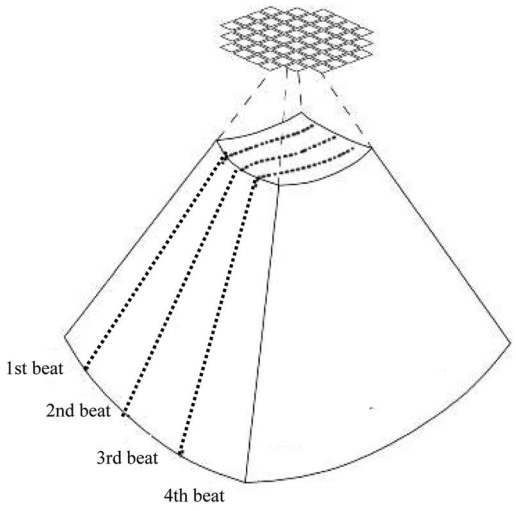


Figure 1 During 3D data acquisition four 20 x 80° sectors are scanned during four consecutive heart beats that are integrated automatically into a 80 x 80° pyramid.

All desired LV anatomical images can be cropped out of the pyramidal volumetric data set after which regional LV wall motion can be assessed. Analysis of LV wall segments can be done according to the 17-segment model recommended by the American Society of Echocardiography (4), but with 3D more detailed models (incorporating for example short axis views) can also be designed. For off-line analysis, the TomTec 4D Echo-View system

(TomTec GmbH, Unterschleissheim, Germany) or the Qlab system (Philips Medical Systems, Andover, Massachussets, USA) can be used.

BENEFITS OF RT3DE IMAGING

RT3DE has several advantages over conventional 2D echocardiographic methods. While 2D echocardiography makes incorrect geometric assumptions about LV morphology, 3D echocardiography sees the LV as it truly is (5). The introduction of new generation RT3DE systems has improved 3D data acquisition and LV volume analysis to a great extent. Importantly, compared to other 3D imaging modalities such as magnetic resonance imaging or computed tomography, RT3DE is easy to learn and a less time consuming imaging modality. As pointed out on earlier, RT3DE has excellent correlation with cardiac magnetic resonance imaging for evaluation of LV volume, mass and ejection fraction with comparable reproducibility (6-8).

With stress RT3DE, at each stress level only one 3D data acquisition from one window is needed instead of multiple 2D data acquisitions from multiple windows. This makes a 3D examination faster than conventional 2D stress imaging. This allows for faster acquisition protocols and/or repeated acquisitions to optimize image quality. From the acquired 3D volumetric data sets, matching views at baseline and at different levels of stress can be selected for a precise comparison of identical segments. Importantly, foreshortened acquired LV walls can be corrected by rotating the 3D data set. RT3DE allows analysis of similar segments in more detail from different planes simply by cropping and rotating the 3D volumetric data set helping the identification of small ischemic LV regions (9) (Figures 2 and 3).

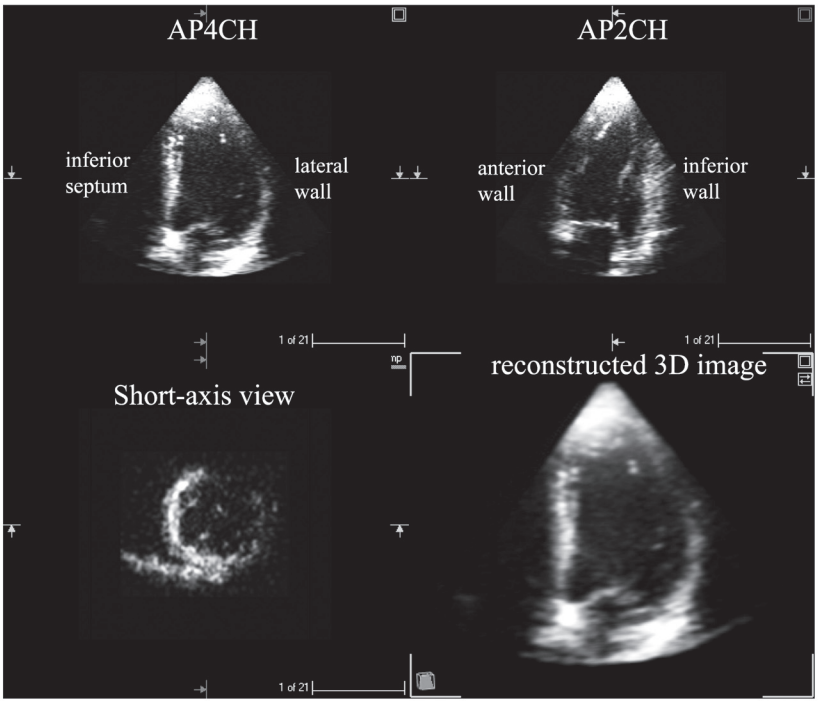


Figure 2 Overview of wall motion produced automatically from a 3D dataset at rest showing apical 4-chamber view (AP4CH, left, top), apical 2-chamber (AP2CH, right, top), cross-sectional short-axis (left, bottom) and reconstructed 3D image (right, bottom).

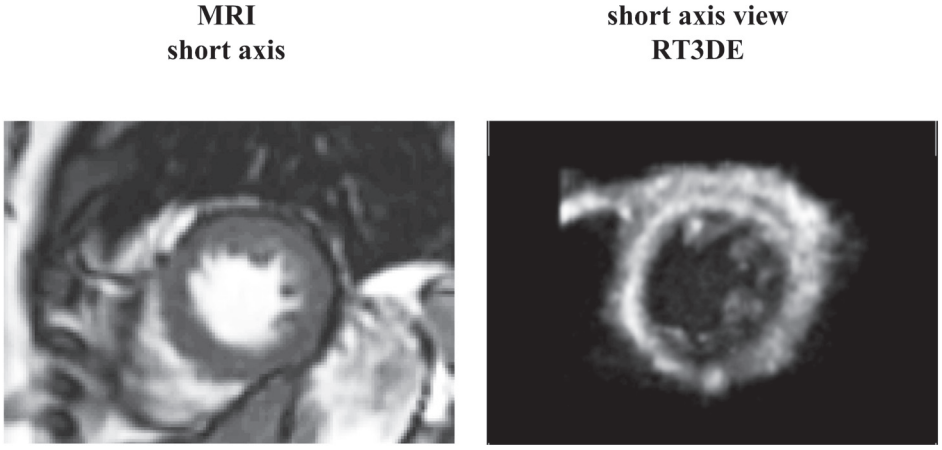


Figure 3 Comparison of left ventricular short axis images at the papillary muscle level in a patient who underwent stress magnetic resonance imaging (MRI) and stress real-time three-dimensional echocardiography (RT3DE). Observe the great similarity in images between RT3DE and MRI.

Some investigators have claimed a higher success rate of adequate image acquisition in the apical region with stress RT3DE compared to 2D echocardiography and the accuracy of

diagnosing myocardial ischemia in the left anterior descending territory tended to be higher by stress RT3DE than by stress 2D echocardiography in one study (9).

RT3DE also allows a more accurate measurement of LV ejection fraction compared to 2D echocardiography (10). Changes in LV ejection fraction during stress may be helpful for the diagnosis of coronary disease and estimation of prognosis (11). Another advantage of RT3DE can be that after the identification of some anatomical landmarks, RT3DE allows automatic calculation of regional volumes that can be another indicator for abnormality (Figure 4).

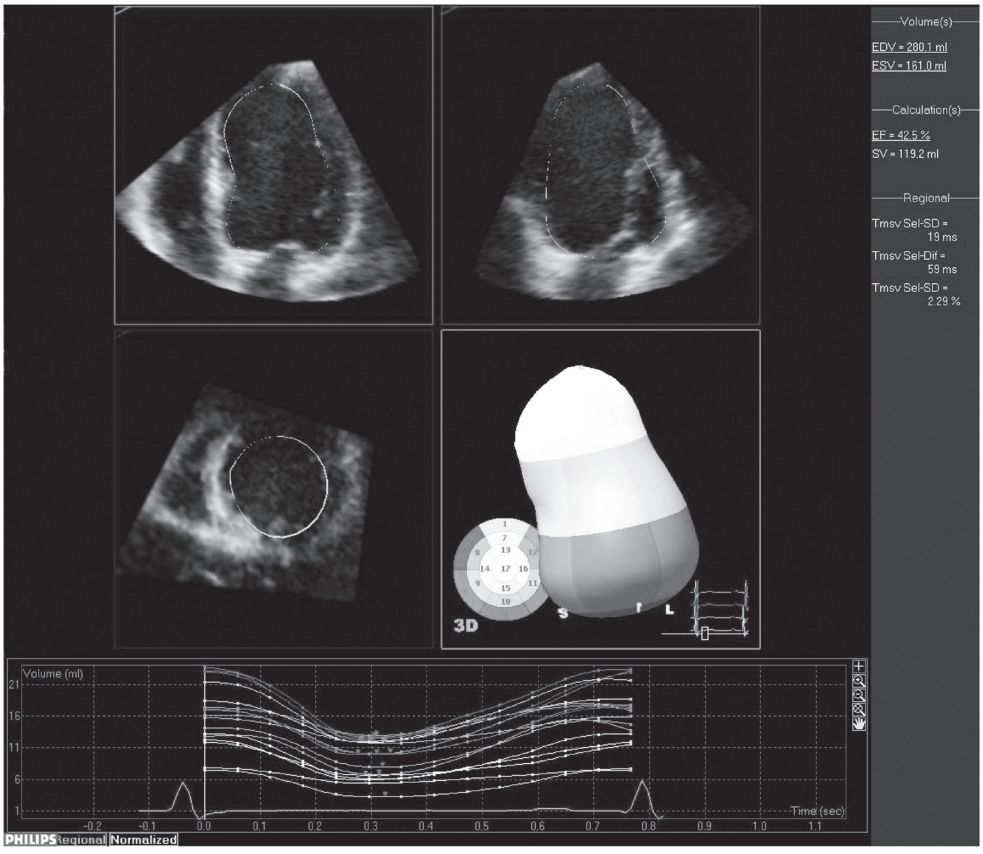


Figure 4 Real-time three-dimensional echocardiography allows the analysis of regional (segmental) wall motion and calculation of volume/time curve of the left ventricle based on semi-automated contour tracings. The volume/time curves of each colour-coded segment in the bull`s eye view (right bottom) are represented in the volume/time curve (bottom)

Finally, RT3DE allows anyplane evaluation of the LV helping to create short-axis views at different LV levels that may be easier to understand by other (non-cardiologists) physicians.

CURRENT LIMITATIONS OF STRESS RT3DE

Notwithstanding its great opportunities, at this moment stress RT3DE has a number of technical limitations. We report on some of these that we encountered with the Philips Sonos 7500 system with the X-4 matrix transducer. Most limitations also apply for the other available 3D systems.

Spatial volume and spatio-temporal resolution. The primary restriction for RT3DE is the limited spatial volume coverage, or actually the trade-off between spatial volume, spatial resolution and temporal resolution (3D frame rate). In analogy to 2D echo, there is a trade-off between frame rate, image depth and number of beams. This limitation is directly related to a physical constant: the speed of sound in human tissue (~1450 m/s). It takes 0.14 msecs to transmit an ultrasound pulse and receive its echoes from a depth of 10 cm. Therefore, only approximately 7500 beams can be acquired per second. With specialized beam forming, multiple beams can be acquired simultaneously, but this goes at the cost of additional artefacts and is bound to practical limits (12). For practical use in echocardiography, the temporal and spatial resolution should satisfy certain minimum requirements. This means that the 3D volume imaged within a time frame is limited. This is the volume we see in the 'live 3D' mode, which is the true real-time 3D mode of the system.

In real practice, to cover the whole LV, four complete heartbeats containing four LV subvolumes have to be recorded. These four LV subvolumes are stitched together to form the total pyramidal LV volume (Figure 1). Actually, 3D image acquisition with the Philips Sonos 7500 system takes seven heart cycles to complete, because some processing is required before

the next beat can be acquired. Slice stitching may give rise to discontinuities at the slice edges (Figure 5).

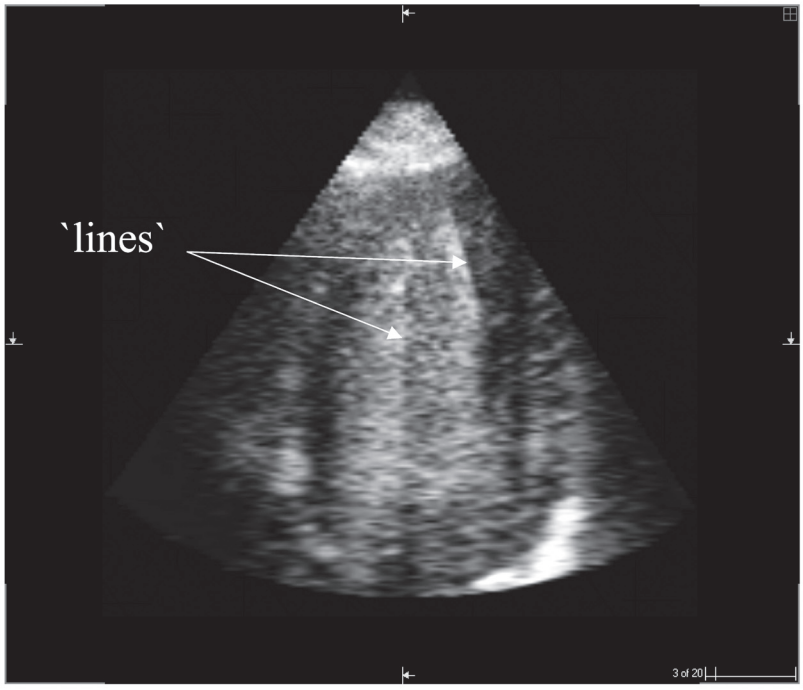


Figure 5 Slice stitching may give rise to discontinuities at the slice edges.

3D image slice discontinuities may be aggravated by transducer or patient motion (prominent breathing motion at peak stress), variations in heart rate (during stress the latest recorded beat may be shorter in duration), arrhythmias and imperfect electrocardiographic triggering. Unfortunately, irregular heart rhythms (extra-systolic beats, atrial fibrillation) are not seldom encountered during dobutamine stress (1).

Poor anterior wall visualization. Visualization of the LV anterior wall can sometimes be difficult even during 2D echocardiography. Unfortunately, the anterior wall is inadequately visualized in a considerable number of our stress 3D examinations. In our initial experience approximately half of the anterior wall segments are inadequately visualized (13). Others have reported better results for imaging of the anterior wall (14). However, it should be noticed that

in these studies patients were selected on their image quality (15). As shown in Figure 6, these problems are related to the relatively large footprint of the X4 matrix transducer compared to a standard S3 transducer (24 x 20 vs. 24 x 15 mm), leading to rib shadowing.

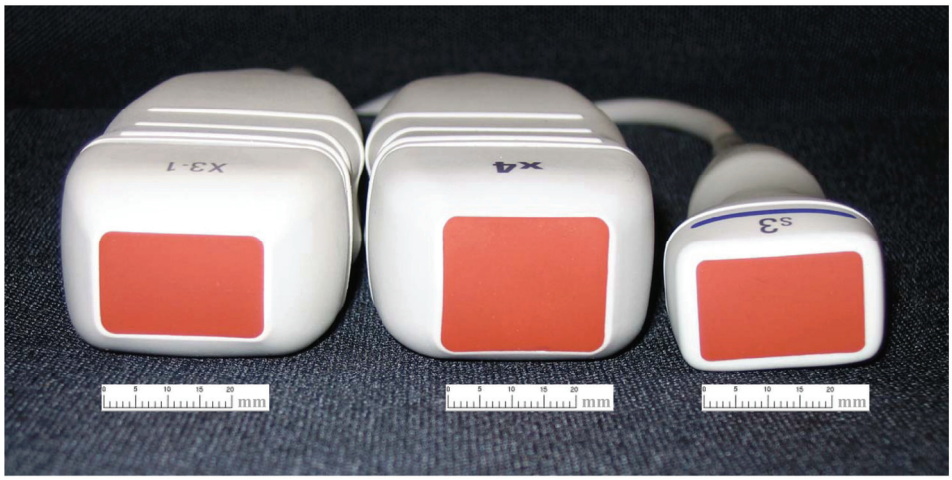


Figure 6 Size of the different Philips transducers, from left to right: 3D-X3-1 (24 x 15 mm), 3D-X4 (24 x 20 mm) and 2D-S3 (24 x 15 mm).

One could try to make an additional recording from a parasternal window to cover the basal and mid anterior wall, but this would eliminate most of the fast recording advantages of RT3DE. Better results may be expected with the new, smaller X3-1 transducer that has a size comparable to the standard S3 transducer (24 x 15 mm).

Quad-screen display. A practical obstacle for the use of stress RT3DE is the lacking possibility of TomTec and Qlab software to display the different stress stages simultaneously in a quad-screen display. Recently, we developed a simple extension program (Stress4Qlab) that allows simultaneous, synchronized viewing of multiple 3D datasets. Information on this program is available upon request. It is to be expected that built-in support for 3D stress echo will be available soon.

Contrast imaging. It has been demonstrated that echo contrast improves endocardial border visualization during stress 2D echocardiography (16). Because of the earlier described relative poor quality of 3D images contrast may be an essential part of stress RT3DE (Figure 7).

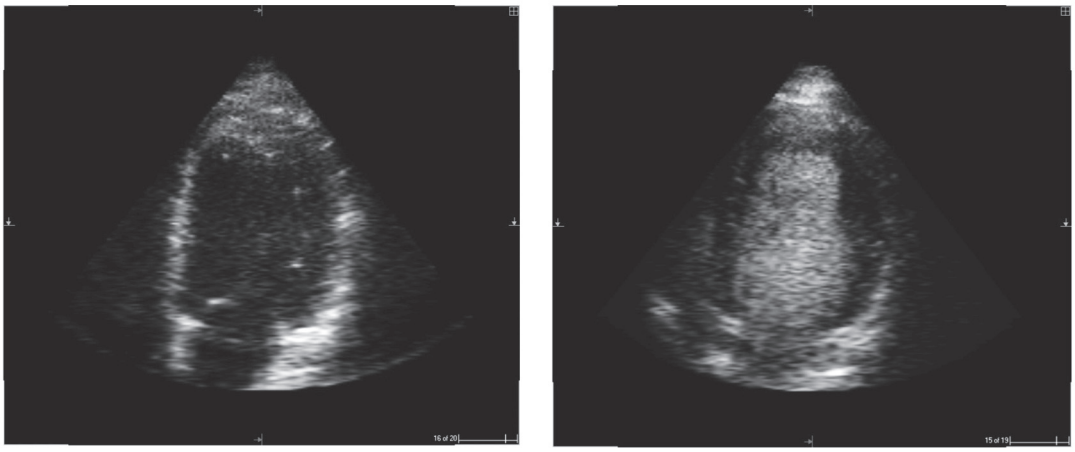


Figure 7 Improvement of endocardial delineation by the use of contrast agent (compare unenhanced (left side) and contrast-enhanced (right side) left ventricular long-axis planes).

However, with contrast LV opacification, stitching artefacts may become aggravated and some additional artefacts may appear (17). During the seven-beat acquisition period contrast opacification of the LV may decay significantly because of microbubble insonification. This problem may be less when the contrast agent is continuously infused rather than given as repeated boluses or when the acquisition period is shortened to four beats, as is possible with the new Philips iE33 system. This was apparent in several cases, where neighbouring slices had different levels of contrast opacification, causing sharp transitions at the slice edges. Furthermore, the differentiation between contrast and tissue is not as good as in standard 2D harmonic imaging, because the matrix transducer has a limited relative bandwidth, and is therefore less suitable for harmonic imaging.

A minor additional problem is the brighter appearance of the first frame of a beat compared to the next frames. This is attributable to the fact that there is no acquisition at the

second, fourth and sixth heartbeat, so the first frame of each beat is acquired after a period without insonification. In later frames some contrast will be progressively destroyed by the ultrasound pulse and contrast brightness will be lower.

CLINICAL 3D STRESS ECHOCARDIOGRAPHIC STUDIES

Three-dimensional echocardiography has been available for several years using time-consuming reconstruction techniques. However, recent advances in transducer technology and front-end data processing have brought real-time 3D echocardiography (RT3DE) into clinical practice. In several studies, resting RT3DE was as accurate as magnetic resonance imaging (MRI) in the evaluation of LV morphology and function (5-8).

At this moment, only a few studies have been reported on the clinical value of *stress* RT3DE (see Table 1). In the first published stress RT3DE study by Zwas *et al.* the feasibility of a Volumetrics Medical Imaging RT3DE system (Volumetrics, Durham, North Carolina, USA) during treadmill stress was investigated (18). In this study, 89% of LV segments were visible at peak stress when only an apical window was used to record the 3D data set. This number increased to 98% if in addition to the apical window also a parasternal window was used. Ahmad *et al.* used the same Volumetrics RT3DE system with dobutamine as stressor (19). They confirmed that stress RT3DE is feasible and superior interobserver agreement and diagnostic accuracy was described for stress RT3DE due to more complete visualization of all LV segments in multiple views. Matsumura *et al.* compared stress 2D echocardiography with RT3DE using a second-generation Philips Sonos 7500 3D echocardiography system (Philips Medical Systems, Andover, Massachusetts, USA) equipped with a matrix-array X4 transducer with 3000 active elements (9, 20). In this study, exercise Tl-201 single-photon emission computed tomography served as the reference standard for myocardial ischemia (9). They

confirmed that stress RT3DE offers rapid and simple acquisition of the entire LV wall motion and provides feasible and accurate assessment of myocardial ischemia, comparable to stress 2D echocardiography. Takeuchi *et al.* examined the feasibility of contrast-enhanced dobutamine stress RT3DE compared to stress 2D echocardiography (14). A significantly higher number of good quality, interpretable segments for wall motion analysis was described with contrast-enhanced dobutamine stress RT3DE. However, the concordance for the identification of wall motion abnormalities between stress 2D echocardiography and RT3DE was only modest, in particular because of discordant results noted in the LAD territory. Unfortunately, no gold standard for coronary ischemia was available. The beneficial effects in terms of image quality and interobserver agreement for wall motion scoring of contrast-enhanced dobutamine stress RT3DE was recently confirmed by Pulerwitz *et al.* (21) and our group (13) (see Table 1). The somewhat lower visibility of contrast-enhanced myocardial segments in our study might be explained by the non-selection of our patients (15). Currently, alternative RT3DE systems (GE Vingmed Vivid 7 system with 3V transducer, Philips iE33 system with the X3-1 transducer) are already available and it is expected that systems from other vendors will be introduced soon. Although in some of these first studies stress RT3DE looks promising for the detection of ischemia, more investigations are needed, because the number of studies is limited.

Table 1. Real-Time Three-Dimensional Stress Echocardiographic Studies.

Authors	Stress	RT3DE system	Windows	Segments visible at peak stress (conventional imaging)	Segments visible at peak stress (contrast imaging)	Sensitivity in detecting ischemia (3D vs. 2D)
Zwas (18)	Treadmill	VMI / 2.5 MHz	AP + PS	89% (98%*)	-	-
Ahmad (19)	Dobutamine	VMI / 2.5 MHz	AP + PS	92%*	-	78% vs. 59%#
Matsumura (9)	Dobutamine	Sonos 7500 / 2-4 MHz	AP	89%	-	75% vs. 75%$
Takeuchi (14)	Dobutamine	Sonos 7500 / 2-4 MHz	AP	-	97%	-
Pulerwitz (21)	Dobutamine	Sonos 7500 / 2-4 MHz	AP	75% (87%@)	97% (99%@)	-
Nemes (13)	Dobutamine	Sonos 7500 / 2-4 MHz	AP	76%	90%	-

* including parasternal view analysis. AP = apical. PS = parasternal. VMI = Volumetrics Medical Imaging

Gold standard = # coronary angiography, $ Tl-201 reversible defects, @ including short-axes analysis.

CONCLUSIONS AND FUTURE DEVELOPMENTS

Although stress RT3DE may be well clinical feasible according to some studies (9,18,19,21), in our opinion this imaging modality is currently still hampered by some major technical limitations. However, most of these limitations may be handled with or may be overcome in the near future. Analysis software will be adapted to support stress RT3DE with proper choice of corresponding viewing planes in rest, low-dose and stress with simultaneous synchronized viewing. In addition, future transducers will have larger bandwidth and thus will be more suitable for harmonic imaging and contrast and the transducer footprint size will be further reduced. The 3D-X3-1 transducer on the new iE33 system already has a much smaller footprint that may circumvent rib shadowing.

Multibeat frame composition and limited spatial resolution actually form the major technical limitations. To overcome this, more ultrasound beams have to be processed in parallel. This requires technological innovation, but it will ultimately result in true RT3DE LV visualization. This will seriously extend the possibilities and clinical value of RT3DE, not just for stress RT3DE.

Ultimately, the inherent advantages of stress RT3DE will eliminate some of the current limitations of stress 2D echocardiography, and may result in an improved diagnostic technique (Table 2).

Table 2. Benefits of RT3DE compared to 2D echocardiography

	2D echocardiography	*RT3DE*
Wall motion	+	++
Contrast	++	+
Volumes	+	++
Regional volumes	-	+

+ means clinically available, - means clinically not available

Moreover, with the development of more advanced automated border detection software, we can also expect a decrease in inter-observer variability associated with the visual scoring of segmental wall motion. Also the learning curve to interpret wall motion analysis may become easier because of the 3D nature of the images. If 3D image quality can be brought to a comparable level as 2D image quality, stress RT3DE may be more suitable for such automated analysis than stress 2D echo because 3D images offer a higher information content with complete LV visualization. Provided that all these technical improvements will occur stress RT3DE may become an important diagnostic test of the future.

References

1. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997;30:595-606.
2. Armstrong WF, Zoghbi WA. Stress echocardiography: current methodology and clinical applications. J Am Coll Cardiol 2005;45:1739-1747.
3. Smart SC, Bhatia A, Hellman R, Stoiber T, Krasnow A, Collier BD, et al. Dobutamine-atropine stress echocardiography and dipyridamole sestamibi scintigraphy for the detection of coronary artery disease: limitations and concordance. J Am Coll Cardiol 2000;36:1265-1273.
4. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539-542.
5. Jenkins C, Bricknell K, Hanekom L, Marwick TH. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. J Am Coll Cardiol 2004;44:878-886.
6. van den Bosch AE, Robbers-Visser D, Krenning BJ, McGhie JS, Helbing WA, Meijboom FJ, et al. Comparison of real-time three-dimensional echocardiography to magnetic resonance imaging for assessment of left ventricular mass. Am J Cardiol 2006;97:113-117.
7. van den Bosch AE, Robbers-Visser D, Krenning BJ, Voormolen MM, McGhie JS, Helbing WA, et al. Real-time transthoracic three-dimensional echocardiographic assessment of left ventricular volume and ejection fraction in congenital heart disease. J Am Soc Echocardiogr 2006;19:1-6.
8. Bu L, Munns S, Zhang H, Disterhoft M, Dixon M, Stolpen A, et al. Rapid full volume data acquisition by real-time 3-dimensional echocardiography for assessment of left

ventricular indexes in children: a validation study compared with magnetic resonance imaging. J Am Soc Echocardiogr 2005;18:299-305.
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;26:1625-1632.
10. Arai K, Hozumi T, Matsumura Y, Sugioka K, Takemoto Y, Yamagishi H, et al. Accuracy of measurement of left ventricular volume and ejection fraction by new real-time three-dimensional echocardiography in patients with wall motion abnormalities secondary to myocardial infarction. Am J Cardiol 2004;94:552-558.
11. Olson CE, Porter TR, Deligonul U, Xie F, Anderson JR. Left ventricular volume changes during dobutamine stress echocardiography identify patients with more extensive coronary artery disease. J Am Coll Cardiol 1994;24:1268-1273.
12. Hergum T, Bjastad T, Torp H. Parallel beamforming using Synthetic Transit Beams. In: proceedings IEEE Ultrasonics symposium; 2004; 2004. p. 1401-1404.
13. Nemes A, Geleijnse ML, Krenning BJ, Soliman OII, Anwar AM, Vletter WB, et al. Usefulness of Ultrasound Contrast Agent to Improve Image Quality During Real-Time Three-Dimensional Stress Echocardiography. Am J Cardiol 2007;99:275-278.
14. Takeuchi M, Otani S, Weinert L, Spencer KT, Lang RM. 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;19:294-299.
15. Geleijnse ML, Nemes A, Vletter WB. Contrast-enhanced Real-time 3-Dimensional Dobutamine Stress Echocardiography. J Am Soc Echocardiogr 2006;19:1076.
16. Dolan MS, Riad K, El-Shafei A, Puri S, Tamirisa K, Bierig M, 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;142:908-915.
17. Voormolen MM, Bouakaz A, Krenning BJ, Lancee CT, ten Cate FJ, de Jong N. Feasibility of 3D harmonic contrast imaging. Ultrasonics 2004;42:739-743.
18. Zwas DR, Takuma S, Mullis-Jansson S, Fard A, Chaudhry H, Wu H, et al. Feasibility of real-time 3-dimensional treadmill stress echocardiography. J Am Soc Echocardiogr 1999;12:285-289.
19. Ahmad M, Xie T, McCulloch M, Abreo G, Runge M. Real-time three-dimensional dobutamine stress echocardiography in assessment stress echocardiography in assessment of ischemia: comparison with two-dimensional dobutamine stress echocardiography. J Am Coll Cardiol 2001;37:1303-1309.
20. Franke A, Kuhl HP. Second-generation real-time 3D echocardiography: a revolutionary new technology. MedicaMundi 2003;47:34-40.
21. Pulerwitz T, Hirata K, Abe Y, Otsuka R, Herz S, Okajima K, et al. Feasibility of Using a Real-time 3-Dimensional Technique for Contrast Dobutamine Stress Echocardiography. J Am Soc Echocardiogr 2006;19:540-545.

CHAPTER 6

Usefulness of Ultrasound Contrast Agent to Improve Image Quality During Real-Time Three-Dimensional Stress Echocardiography

American Journal of Cardiology 2007; 99: 275-278

Attila Nemes

Marcel L. Geleijnse

Boudewijn J. Krenning

Osama I.I. Soliman

Ashraf M. Anwar

Wim B. Vletter

Folkert J. ten Cate

Abstract

Dobutamine stress echocardiography is an accepted tool for the diagnosis of coronary artery disease. Some investigators have claimed that three-dimensional imaging improves the diagnostic accuracy of dobutamine stress echocardiography. The purpose of the present investigation was to examine the role of echo contrast in the improvement of segmental quality and inter-observer agreement during stress real-time 3D echocardiography (RT3DE). The study comprised 36 consecutive patients with stable chest pain referred for routine stress testing. The 3D images were acquired with a RT3DE system with X4 matrix array transducer. All available reconstructed 2D segments were graded as optimal, good, moderate and poor. Wall motion was scored as normal, mild hypokinesia, severe hypokinesia, akinesia and dyskinesia. At peak stress, 466 of the 612 segments (76%) could be analysed during conventional RT3DE. With contrast-enhanced RT3DE, the number of available segments increased to 553 (90%). The image quality index during conventional RT3DE was 2.2, while with contrast-enhanced RT3DE 3.1. With conventional RT3DE, the two independent observers agreed on the diagnosis of myocardial ischaemia in 85 of 108 coronary territories (79%, κ = 0.26). With contrast-enhanced RT3DE, it increased to 95 of 108 coronary territories (88%, κ = 0.59). Study agreement on myocardial ischaemia was present in 26 of 36 studies (72%, κ = 0.43) with conventional RT3DE, and in 32 of 36 studies (89%, κ = 0.77) with contrast-enhanced RT3DE. In conclusion, during stress RT3DE contrast-enhanced imaging significantly decreases the number of poorly visualized myocardial segments and improves interobserver agreement for the diagnosis of myocardial ischemia.

Introduction

Dobutamine stress echocardiography is an accepted tool for the diagnosis of coronary artery disease (1). The interpretation of the echocardiographic images, however, is critically dependent on the quality of the recordings and the experience of the observer (2). Some investigators have claimed that three-dimensional imaging improves the diagnostic accuracy of dobutamine stress echocardiography (3-5). However, one of the main limitations of three-dimensional imaging is the inherently lower image quality compared to two-dimensional imaging. Left ventricular (LV) opacificating contrast agents have been successfully applied during 2-dimensional dobutamine stress echocardiography to improve endocardial border delineation (6). The use of intravenous ultrasound contrast improves endocardial border visualization, leading to a more accurate interpretation of wall motion abnormalities (6). The purpose of the present investigation was to examine the role of echo contrast in the improvement of LV segmental quality and interobserver agreement during stress real-time three-dimensional echocardiography (RT3DE).

Patients and methods

Patient population. The study comprised 36 consecutive patients in sinus rhythm with chest pain referred for stress testing. Baseline clinical characteristics of the patients are presented in Table 1. Beta-blockers were used in 22 patients (61%). The study was approved by the institutional review board and all patients gave informed consent.

Table 1 Clinical and demographic characteristics (n = 36)

Variable	Subjects
Age (years)	57 ± 13
Men	24 (67%)
Diabetes mellitus	9 (25%)
Hypertension *	18 (50%)
Hypercholesterolemia †	14 (39%)
Current smoker	4 (11%)
Prior acute myocardial infarction	10 (28%)
Prior coronary bypass surgery	2 (6%)
Prior coronary angioplasty	7 (19%)

* Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.

† Defined as total serum cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or the use of a lipid-lowering agent.

Dobutamine-atropine stress protocol. Dobutamine was administered through a peripheral vein by three-minute stages of 10, 20, 30 and 40 μg/kg/min, respectively. The infusion was stopped when 85% of age-predicted heart rate was reached. Otherwise, dobutamine infusion was continued and supplemented by 0.25 mg doses of atropine (to a maximal dose of 1 mg). The stress test was terminated when severe angina, shortness of breath, symptomatic decrease in systolic blood pressure (>40 mm Hg), arterial hypertension (>240/120 mm Hg), severe arrhythmias or other serious adverse effects occurred.

The contrast examination. Sonovue (Bracco, Milan, Italy) was used at baseline conditions, low-dose and peak stress. The contrast agent was given as a bolus of 0.5 ml with additional boluses of 0.25 ml when needed. A low mechanical index (0.3) was used. Care was taken to record the images at a phase when contrast flow was relatively stable with absent or minimal swirling of contrast in the apex.

Real-time three-dimensional dobutamine stress echocardiography. The RT3DE images were acquired from an apical window with a Sonos 7500 echo system (Philips Medical Systems, Best, The Netherlands) equipped with a 3D data acquisition software package. X4 matrix array transducer was attached to the echocardiograph. After visualizing the reference images (the apical four-chamber and orthogonal views) a full volume data set of the LV was acquired. With electrocardiographic gating four pyramidal subvolumes of ~20x80° were acquired during the first, third, fifth, and seventh cardiac cycle. These four conical subvolumes were automatically integrated into a pyramidal data set of ~80x80° incorporating full LV volume. Regional LV wall motion was evaluated using cropped planes representative of the 4-chamber, 2-chamber, and 3-chamber view.

Off-line data analysis: The digitally stored RT3DE data set was analysed off-line with assistance of 4D TomTec Echo-View 5.3 software (TomTec Inc., Unterschleissheim, Germany). The RT3DE data set was judged on the basis of the absence of artefacts throughout the cardiac cycle. All at peak stress available reconstructed segments were graded as optimal (excellent quality without possibility to improve - 4), good (good quality without artefacts - 3), moderate (sufficient quality without artefacts or good quality with artefact - 2) or poor (poor or moderate quality with artefacts - 1). An image quality index was calculated for each segment by summation of all scores in that particular segment divided by the number of analysed

segments. Wall motion was assessed using the standard 17-segment LV model of the 3 reconstructed apical views by two independent observers who were blinded to the patient's clinical data (7). Wall motion was scored as normal, mild hypokinesia, severe hypokinesia, akinesia and dyskinesia. A test was considered positive in case of new or worsening wall motion abnormalities at any stage during stress. Segmental wall motion abnormalities were assigned to coronary artery territories as described before (1).

Statistical analysis. All values were expressed as a mean ± SD. The Student *t* test was used to compare the difference between tests. The kappa (κ) coefficient was calculated to determine interobserver agreement. A kappa value <0.4 was considered poor, 0.4 to 0.7 moderate, and >0.7 good. Data were analyzed using standard statistical software (SPSS, version 12.0, Chicago, Illinois).

Results

Dobutamine stress data. Heart rate increased from 71 ± 13 to 124 ± 23 bpm and systolic blood pressure from 128 ± 21 to 140 ± 29 mm Hg. No significant side effects were encountered during the dobutamine stress contrast study.

Myocardial segmental visibility. At peak stress, 466 of the 612 segments (76%) could be analysed during conventional stress RT3DE. With contrast-enhanced stress RT3DE, the number of available LV segments increased to 553 (90%). Non-visualized LV segment distribution during conventional and contrast-enhanced stress RT3DE is depicted in Figure 1.

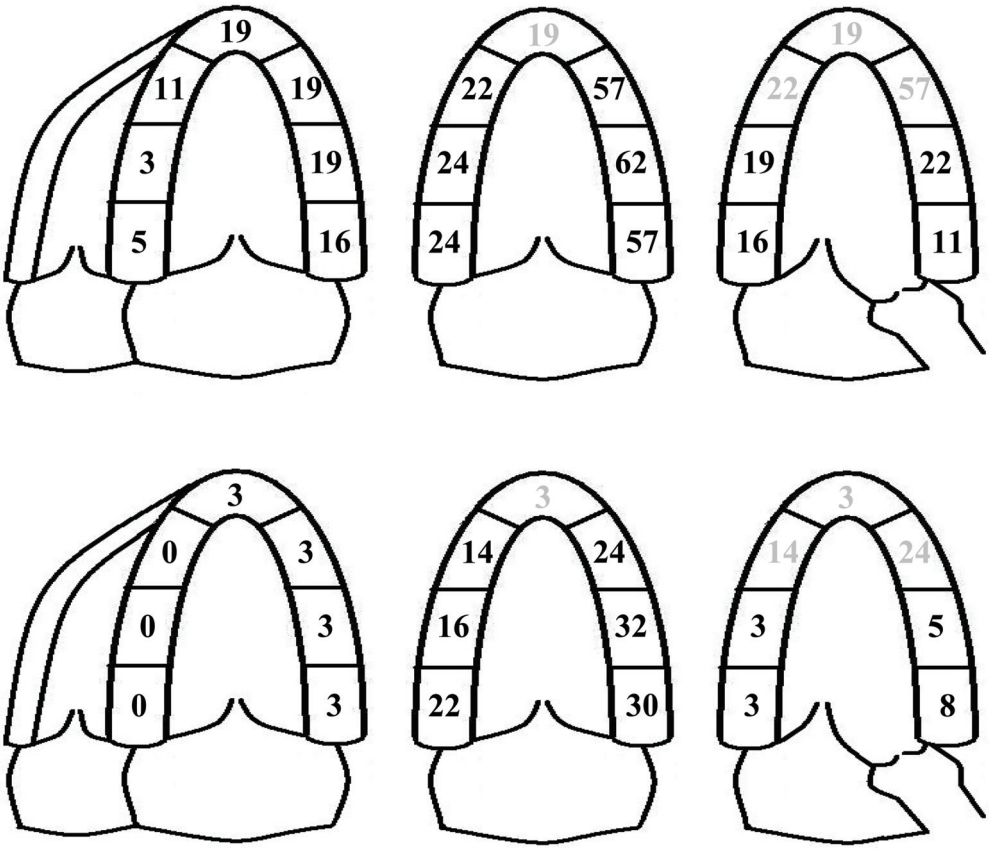


Figure 1 Left ventricular 17-segments model showing the percentage of non-visualized segments during peak stress with conventional (top) and contrast-enhanced (bottom) three-dimensional echocardiography.

Myocardial segment image quality. The image quality index of the 466 analysable segments during conventional stress RT3DE was 2.2. With contrast-enhanced stress RT3DE the image quality index in the 553 analysable segments was 3.1. The quality index distribution of the visualized segments during conventional and contrast-enhanced stress RT3DE is depicted in Figure 2.

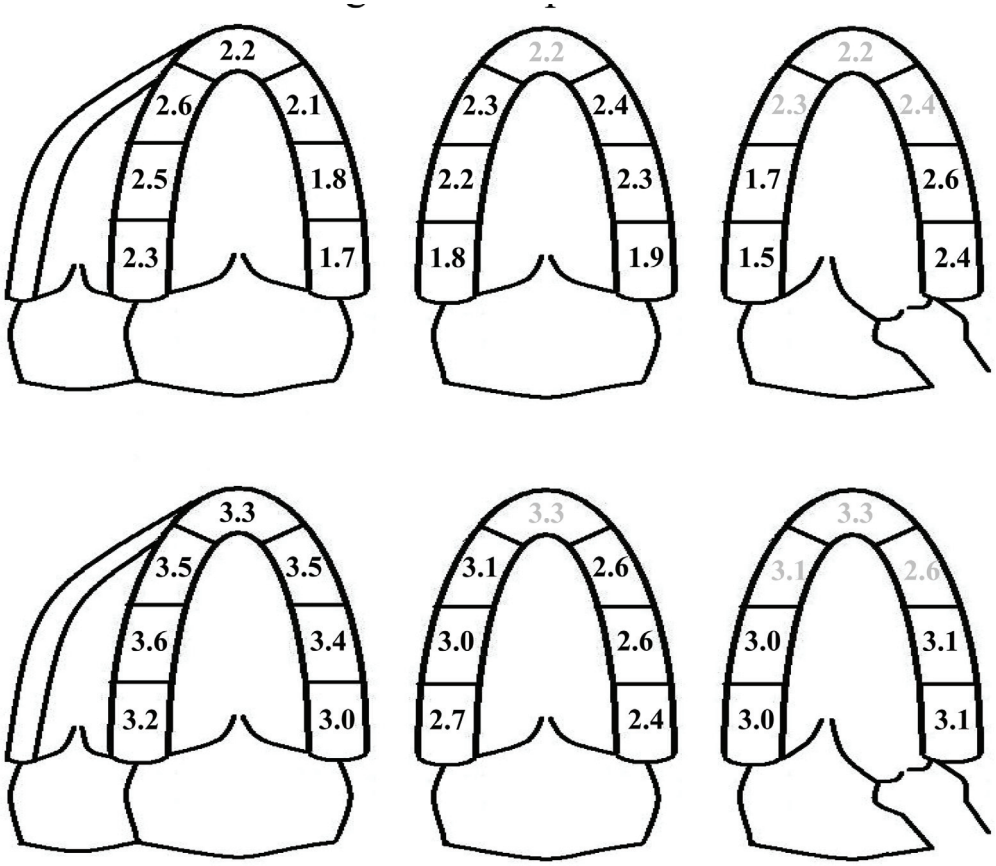


Figure 2 Left ventricular 17-segments model showing the segmental quality index in the visualized segments during peak stress with conventional (top) and contrast-enhanced (bottom) at peak stress three-dimensional echocardiography.

Interobserver agreement for ischaemia. As seen in Figure 3, with conventional stress RT3DE the two observers agreed on the diagnosis of myocardial ischaemia in 85 of 108 coronary territories (agreement 79%, $\kappa = 0.26$). With contrast-enhanced stress RT3DE, the two observers agreed on the diagnosis of myocardial ischaemia, in 95 of 108 coronary territories (agreement 88%, $\kappa = 0.59$). Study agreement on myocardial ischaemia was present in 26 of 36 studies (agreement 72%, $\kappa = 0.43$) with conventional stress RT3DE, and in 32 of 36 studies (agreement 89%, $\kappa = 0.77$) with contrast-enhanced stress RT3DE.

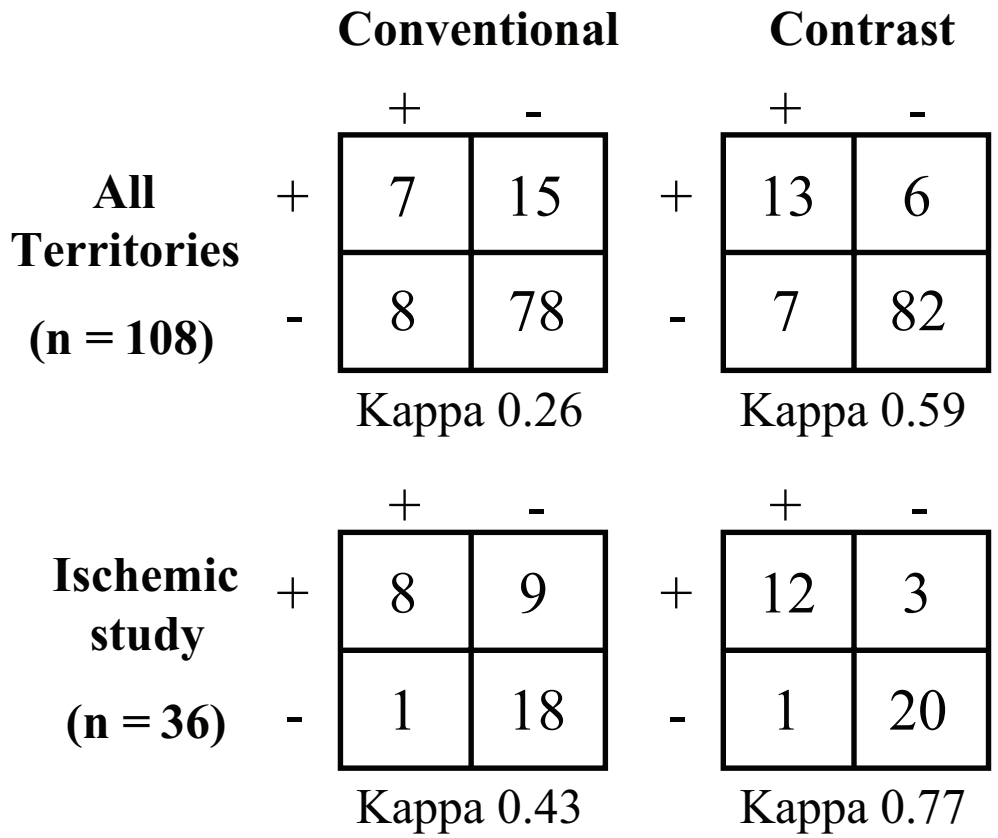


Figure 3 Interobserver agreement with conventional (left) and contrast-enhanced (right) three-dimensional stress echocardiography for the diagnosis of myocardial ischemia for all coronary territories (top) and the overall study result (bottom).

Discussion

The major findings in this study are: [1] a relatively high number of myocardial segments are poorly visualized with conventional stress RT3DE, [2] contrast-enhanced imaging significantly decreases the number of poorly visualized myocardial segments and [3] contrast-enhanced imaging improves interobserver agreement for diagnosis of myocardial ischemia.

Two-dimensional dobutamine stress echocardiography is based on the detection of stress-induced wall motion abnormalities and is an important clinical tool for the detection of coronary artery disease (1). For the detection of wall motion abnormalities endocardial border visualization is essential. However, an important number of patients have suboptimal echo windows (6). Second harmonic imaging (8,9) and contrast echocardiography (6,10) are known to enhance LV endocardial visualization during 2-dimensional dobutamine stress

echocardiography. Because of the trade off between frame rate, image depth and number of beams, RT3DE image quality is inherently lower compared to two-dimensional imaging. Therefore, contrast imaging may be expected to play a major role in improvement of RT3DE image quality.

In our non-selected patients 24% of LV wall segments could not be visualized at conventional peak stress RT3DE. In particular, anterior wall segments were poorly visualized. Obviously, this is an important limitation for conventional stress RT3DE because this wall is crucial for the diagnosis of left anterior descending disease. Apart from an inherently lower quality of three-dimensional imaging, the large X4 transducer footprint (24x20 mm) may be responsible for this limitation. As seen in Table 2, our results of conventional RT3DE imaging look unfavourable compared to other published studies (3-5,11,12). It should, however, be noticed that we studied non-selected patients whereas in other studies patients with poor two-dimensional image quality were excluded from analysis (4,11).

Contrast stress RT3DE substantially decreased the number of non-visualized LV segments and the quality of the visible LV segments was markedly higher. These results confirm the value of contrast use for stress RT3DE recently published by Pulerwitz *et al.* in a very small group of 14 patients (11). Importantly, our study is the first in which it is shown that the improved visibility of segments at peak RT3DE stress improves interobserver agreement for the diagnosis of myocardial ischemia in coronary territories with κ-values that improved from poor to moderate and for the overall diagnosis of myocardial ischemia with κ-values that improved from moderate to good. Notwithstanding our promising results on contrast stress RT3DE new, better transducer technology seems necessary to bring stress RT3DE into clinical practice.

Table 2. Segments visible at peak stress with apical real-time three-dimensional stress echocardiography.

Authors	Patients	Stress	RT3DE system	Segments visible with conventional imaging	Segments visible with contrast imaging
Zwas et al. (5)	20	Treadmill	Volumetrics MI	89% - 98%*	NA
Ahmad et al. (4)	253	Dobutamine	Volumetrics MI	92%*	NA
Matsumura et al. (3)	56	Dobutamine	Sonos 7500 / X4 probe	89%	NA
Takeuchi et al. (12)	78	Dobutamine	Sonos 7500 / X4 probe	NA	97%
Pulerwitz et al. (11)	14	Dobutamine	Sonos 7500 / X4 probe	75% - 87%#	97% - 99%#
Present study	36	Dobutamine	Sonos 7500 / X4 probe	76%	90%

* Segment visible when also the parasternal window was used. MI = Medical Imaging. NA = not available.
# short axis views were used

References

1. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997;30:595-606.
2. 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;17:666-669.
3. 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;26:1625-1632.
4. Ahmad M, Xie T, McCulloch M, Abreo G, Runge M. Real-time three-dimensional dobutamine stress echocardiography in assessment stress echocardiography in assessment of ischemia: comparison with two-dimensional dobutamine stress echocardiography. J Am Coll Cardiol 2001;37:1303-1309.
5. Zwas DR, Takuma S, Mullis-Jansson S, Fard A, Chaudhry H, Wu H, et al. Feasibility of real-time 3-dimensional treadmill stress echocardiography. J Am Soc Echocardiogr 1999;12:285-289.
6. Dolan MS, Riad K, El-Shafei A, Puri S, Tamirisa K, Bierig M, 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;142:908-915.
7. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539-542.
8. Senior R, Soman P, Khattar RS, Lahiri A. Improved endocardial visualization with second harmonic imaging compared with fundamental two-dimensional echocardiographic imaging. Am Heart J 1999;138:163-168.
9. Sozzi FB, Poldermans D, Bax JJ, Boersma E, Vletter WB, Elhendy A, et al. Second harmonic imaging improves sensitivity of dobutamine stress echocardiography for the diagnosis of coronary artery disease. Am Heart J 2001;142:153-159.
10. Falcone RA, Marcovitz PA, Perez JE, Dittrich HC, Hopkins WE, Armstrong WF. Intravenous albunex during dobutamine stress echocardiography: enhanced localization of left ventricular endocardial borders. Am Heart J 1995;130:254-258.
11. Pulerwitz T, Hirata K, Abe Y, Otsuka R, Herz S, Okajima K, et al. Feasibility of Using a Real-time 3-Dimensional Technique for Contrast Dobutamine Stress Echocardiography. J Am Soc Echocardiogr 2006;19:540-545.
12. Takeuchi M, Otani S, Weinert L, Spencer KT, Lang RM. 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;19:294-299.

CHAPTER 7

Role of Parasternal Data Acquisition During Contrast Enhanced Real-Time Three-Dimensional Echocardiography

submitted

Attila Nemes

Marcel L. Geleijnse

Wim B. Vletter

Boudewijn J. Krenning

Osama I.I. Soliman

Folkert J. ten Cate

Abstract

Background. Recent technical developments have resulted in high-resolution real-time three-dimensional echocardiography (RT3DE). The purpose of this study was to investigate the beneficial role of parasternal-acquired images in addition to apical-acquired images during contrast stress RT3DE.

Methods. The study comprised 30 consecutive patients (52 ± 11 years, 18 males) with chest pain referred for routine stress testing. The contrast RT3DE images were acquired from the apical and parasternal window with a Sonos 7500 echo system (Philips Medical Systems, Best, The Netherlands) attached to a X4 matrix array transducer.

Results. From the apical and parasternal acquisition, 464 segments (91%) and 267 segments (52%) could be analysed, respectively (P <0.001). From the apical window, more basal segments were not analysable (22 of 180, 12% vs. 24 of 330, 7%; P =0.06). From the parasternal window, more apical segments were not analysable (117 of 150, 78% vs. 126 of 360, 35%; P <0.01). The mean image quality index of the 464 analysable segments from the apical-acquired images was 2.43. Fourteen out of 180 basal segments (8%), 12 out of 180 mid-ventricular segments (7%) and 2 out of 150 apical segment (1%) were only available with parasternal data acquisition. In addition to these 28 segments, 79 segments (17%) already visualised from the apical window improved in quality. The overall mean image quality index, now assessed from 492 (96%) of all segments, using both the apical and parasternal acquired data, improved to 2.74 (P <0.05).

Conclusions. Addition of parasternal to apical acquisition of contrast RT3DE data can decrease the number of non-visualised segments and improve mean image quality.

Introduction

Recent technical developments have resulted in high-resolution real-time three-dimensional echocardiography (RT3DE) transducers that allow quick acquisition of cardiac images from a single acoustic window (1). Unfortunately, this technique is still limited by the inherently lower image quality compared to 2D imaging. It has been shown by others and us that the use of contrast during stress RT3DE improves image quality and interobserver variability in identifying wall motion abnormalities (2,3). Despite this improvement stress contrast RT3DE is still hampered by non-visible left ventricular (LV) segments or segments with suboptimal image quality, in particular in the anterior (2,3) and lateral wall (2). One of the causes for the suboptimal image quality of these walls may be the relatively large footprint of the 3D transducer. Interfering ribs may block echo beams and cause a partially empty 3D data set. Smaller footprints or acquiring data from a second window, such as the parasternal window, may eliminate these limitations. The purpose of this study was to investigate the beneficial role of parasternal-acquired images in addition to the normal apical-acquired images.

Patients and methods

Patient population: The study comprised 30 consecutive patients (52 ± 11 years, 18 males) in sinus rhythm with chest pain referred for routine stress testing. The institutional review board approved the study and all patients gave informed consent.

The contrast examination: Sonovue (Bracco, Milan, Italy) was used at baseline conditions, low-dose and peak stress. The contrast agent was given as a bolus of 0.5 ml with additional boluses of 0.25 ml when needed. A low mechanical index (0.3) was used. Care was taken to

record the images at a phase when contrast flow was relatively stable with absent or minimal swirling of contrast in the apex.

Real-time three-dimensional dobutamine stress echocardiography: Dobutamine was infused according to the standard protocol (4). The RT3DE images were acquired from the apical and parasternal window with a Sonos 7500 echo system (Philips Medical Systems, Best, The Netherlands) attached to a X4 matrix array transducer. After visualizing the reference images (the apical four-chamber and orthogonal views) a full volume data set of the LV was acquired. With electrocardiographic gating four pyramidal subvolumes of ~20x80° were acquired during the first, third, fifth, and seventh cardiac cycle. These four conical subvolumes were automatically integrated into a pyramidal data set of ~80x80° incorporating full LV volume. In all patients, regional LV wall motion was evaluated using cropped long-axis and short-axis views at three different levels: above the mitral valve, at the papillary muscle level and at the apex.

Off-line data analysis: The digitally stored RT3DE data set was analysed off-line with assistance of QLAB software (Philips, Best, the Netherlands). The RT3DE data set was judged on the basis of the absence of artefacts throughout the cardiac cycle. All available reconstructed segments were graded as optimal (excellent quality without possibility to improve - 4), good (good quality without artefacts - 3), moderate (sufficient quality without artefacts or good quality with artefact - 2) or poor (poor or moderate quality with artefacts - 1). An image quality index was calculated for each segment by summation of all scores in that particular segment divided by the number of analysed segments. The attribution of the different myocardial segments to the coronary arteries was done according to current guidelines and is displayed in Figure 1 (5).

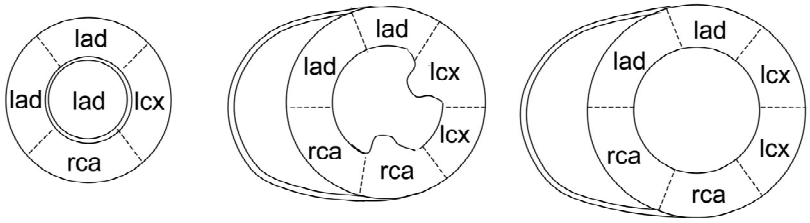


Figure 1. Attribution of the different myocardial segments to the different coronary arteries.

Statistical analysis: All values were expressed as a mean ± SD. The Student *t* test was used to compare the difference between tests. Data were analyzed using standard statistical software (SPSS, version 12.0, Chicago, Illinois).

Results

Myocardial segmental visibility. From the apical and parasternal acquisition, 464 segments (91%) and 267 segments (52%) could be analysed, respectively (P <0.001). The non-visualized LV segment distribution during apical and parasternal data acquisition is depicted in Figure 2.

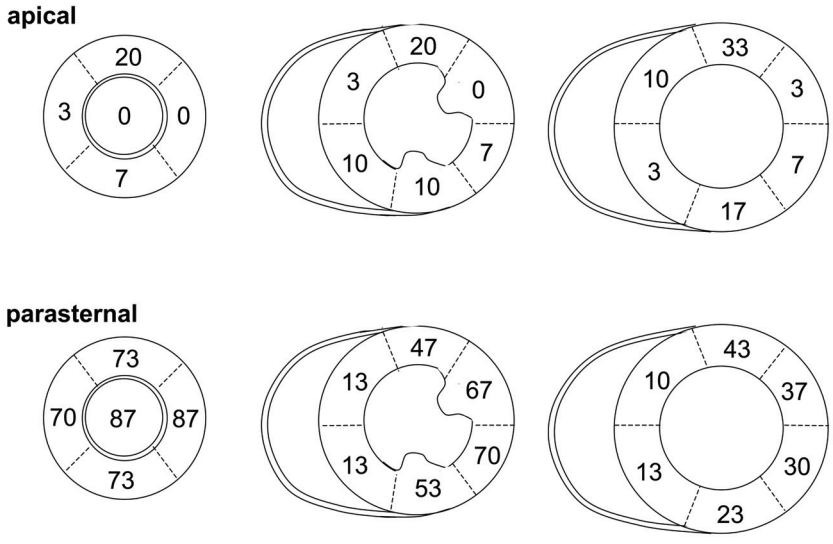


Figure 2. Left ventricular 17-segments model showing the percentage of non-available segments during apical (top) and parasternal (bottom) data acquisition during real-time three-dimensional echocardiography.

With apical-acquired images the percentage of non-analysable segments attributed to the left anterior descending coronary artery was higher compared to the number of non-analysable segments attributed to the left circumflex or right coronary artery (27 of 210, 13% vs. 19 of 300, 6%; P <0.02). With parasternal imaging, the percentage of non-analysable segments attributed to the left anterior descending coronary artery was comparable to the number of non-analysable segments attributed to the left circumflex or right coronary artery (103 of 210, 49% vs. 140 of 300, 47%; P = NS). From the apical window, more basal segments were not analysable (22 of 180, 12% vs. 24 of 330, 7%; P =0.06). From the parasternal window, more apical segments were not analysable (117 of 150, 78% vs. 126 of 360, 35%; P <0.01).

Myocardial segment image quality. The mean image quality index of the 464 analysable segments from the apical-acquired images was 2.43. With parasternal data acquisition the image quality index in the 267 analysable segments was 2.61. The quality index distribution of the visualized segments during apical and parasternal data acquisition is depicted in Figure 3.

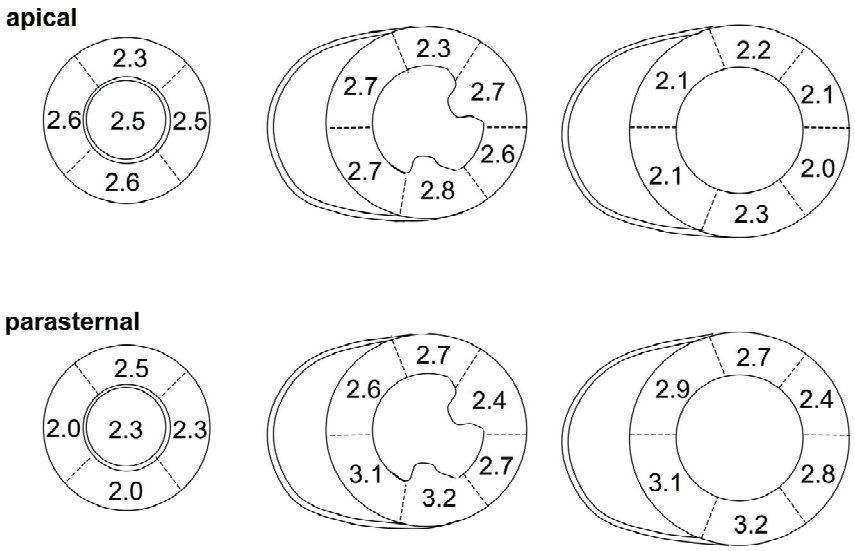


Figure 3. Left ventricular 17-segments model showing the segmental quality index in the visualized segments during apical (top) and parasternal (bottom) data acquisition during real-time three-dimensional echocardiography.

In the analysable segments from the apical window mean quality index was lowest for the basal segments (2.12 basal vs. 2.64 mid and 2.51 apical, all P <0.001, respectively). In the analysable segments from the parasternal window mean quality index was lowest for the apical segments (2.09 apical vs. 2.38 mid, p = 0.07, 2.09 apical vs. 2.66 basal, P <0.01).

Additive value of parasternal acquisition. Fourteen out of 180 basal segments (8%), 12 out of 180 mid-ventricular segments (7%) and 2 out of 150 apical segment (1%) were only available with parasternal data acquisition. The distribution of these segments and their mean quality indices are depicted in Figure 4.

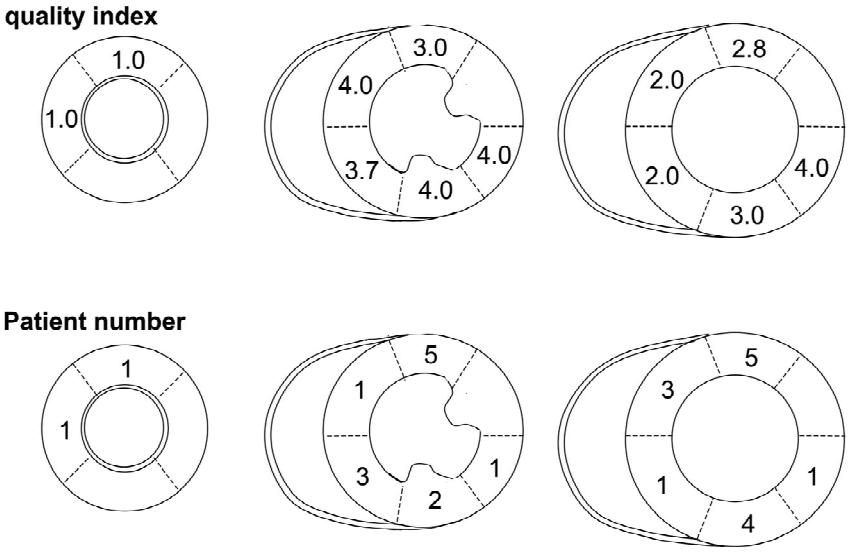


Figure 4. Quality index (top) and segment number (bottom) visible uniquely during parasternal data acquisition.

Mean quality index in these 28 segments was 2.93. In addition to these 28 segments, 79 segments (17%) already visualised from the apical window improved in quality. The overall mean image quality index, now assessed from 492 (96%) of all segments, using both the apical and parasternal acquired data, improved to 2.74 (P <0.05).

Discussion

The major findings in this study are: [1] a substantial number of LV myocardial segments are not visualized during apical-acquired contrast-enhanced stress RT3DE, and [2] addition of parasternal acquisition of RT3DE data can decrease the number of non-visualised segments and improve mean image quality.

Stress echocardiography relies on regional, rather than global, assessment of LV function. Therefore, visibility of as many as possible LV segments at the highest available quality is mandatory. Previously, others and us have shown the value of ultrasound contrast during stress RT3DE to maximize the for analysis available segments and improve image quality (2,3,6). Unfortunately, still a significant number of segments are not visualised during the standard apical acquisition and the image quality is suboptimal. This seems primarily related to the relatively large footprint of the 3D transducer and inherently lower quality of 3D imaging, because of the trade off between frame rate, number of beams, and depth. In addition, the differentiation between contrast and tissue is not as good as in standard 2D harmonic imaging, because the matrix transducer with its limited relative bandwidth is less suitable for harmonic imaging. Additional parasternal data acquisition may offer some advantages. In particular basal segments are known to be imaged suboptimal from the apical window during contrast RT3DE (3,7), whereas these segments are usually the better ones imaged from the parasternal window. In addition, some walls may be better imaged from a parasternal window because of axial rather than lateral resolution.

In our study 9% of all LV segments acquired from the apical window could not be obtained. This number is comparable to the results of Zwas *et al.* who reported that 11% of LV segments acquired from the apical window could not be obtained during treadmill stress 3D echocardiography (8). In particular basal segments and/or segments assigned to the left anterior descending coronary artery were less visualised, confirming previous reports (2,3,7). From the

parasternal window significantly less segments could be visualised. However, 28 segments (5%) could be visualised uniquely from the parasternal-acquired data set with a high image quality index. In particular, a substantial number of basal segments and/or segments assigned to the left anterior descending coronary artery could be visualised only from the parasternal-acquired data set. The total number of visualised segments increased from 464 (91%) from the apical window to 492 (96%) from the apical combined with parasternal window with corresponding mean image quality indices of 2.43 and 2.74, respectively. Unfortunately, this multi-window approach eliminates one of the advantages of stress RT3DE, the rapid acquisition from one single acoustic window. Therefore, future studies should look to the availability and quality of segments acquired from only the apical window with the new, smaller X3-1 matrix transducer and re-assess the necessity of the addition of a second window.

Conclusion

Stress echocardiography depends on regional wall motion analysis. With contrast stress RT3DE inclusion of both apical and parasternal acquired images in the data set is essential to increase the number of visualized segments and to improve overall image quality.

References

1. Franke A, Kuhl HP. Second-generation real-time 3D echocardiography: a revolutionary new technology. MedicaMundi 2003;47:34-40.
2. Takeuchi M, Otani S, Weinert L, Spencer KT, Lang RM. 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;19:294-299.
3. Nemes A, Geleijnse ML, Krenning BJ, Soliman OII, Anwar AM, Vletter WB, et al. Usefulness of Ultrasound Contrast Agent to Improve Image Quality During Real-Time Three-Dimensional Stress Echocardiography. Am J Cardiol 2007;99:275-278.
4. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997;30:595-606.

5. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539-542.
6. Pulerwitz T, Hirata K, Abe Y, Otsuka R, Herz S, Okajima K, et al. Feasibility of Using a Real-time 3-Dimensional Technique for Contrast Dobutamine Stress Echocardiography. J Am Soc Echocardiogr 2006;19:540-545.
7. Kasprzak JD, Paelinck B, Ten Cate FJ, Vletter WB, de Jong N, Poldermans D, et al. Comparison of native and contrast-enhanced harmonic echocardiography for visualization of left ventricular endocardial border. Am J Cardiol 1999;83:211-217.
8. Zwas DR, Takuma S, Mullis-Jansson S, Fard A, Chaudhry H, Wu H, et al. Feasibility of real-time 3-dimensional treadmill stress echocardiography. J Am Soc Echocardiogr 1999;12:285-289.

CHAPTER 8

Dobutamine Stress MRI versus Three-Dimensional Contrast Echocardiography: It's All Black & White

submitted

Attila Nemes

Marcel L. Geleijnse

Robert-Jan van Geuns

Osama I.I. Soliman

Wim B. Vletter

Boudewijn J. Krenning

Folkert J. ten Cate

Abstract

Dobutamine stress magnetic resonance imaging is considered the superior stress modality to detect wall motion abnormalities. In this report we demonstrate the strengths of a newly developed stress modality: dobutamine stress contrast-enhanced real-time three-dimensional echocardiography. This stress modality may become a competitor for stress magnetic resonance imaging allowing fast acquisition and an unlimited number of left ventricular cross-sections. Unfortunately, at this moment adequate imaging with stress real-time three-dimensional echocardiography is only possible in the minority of cardiac patients.

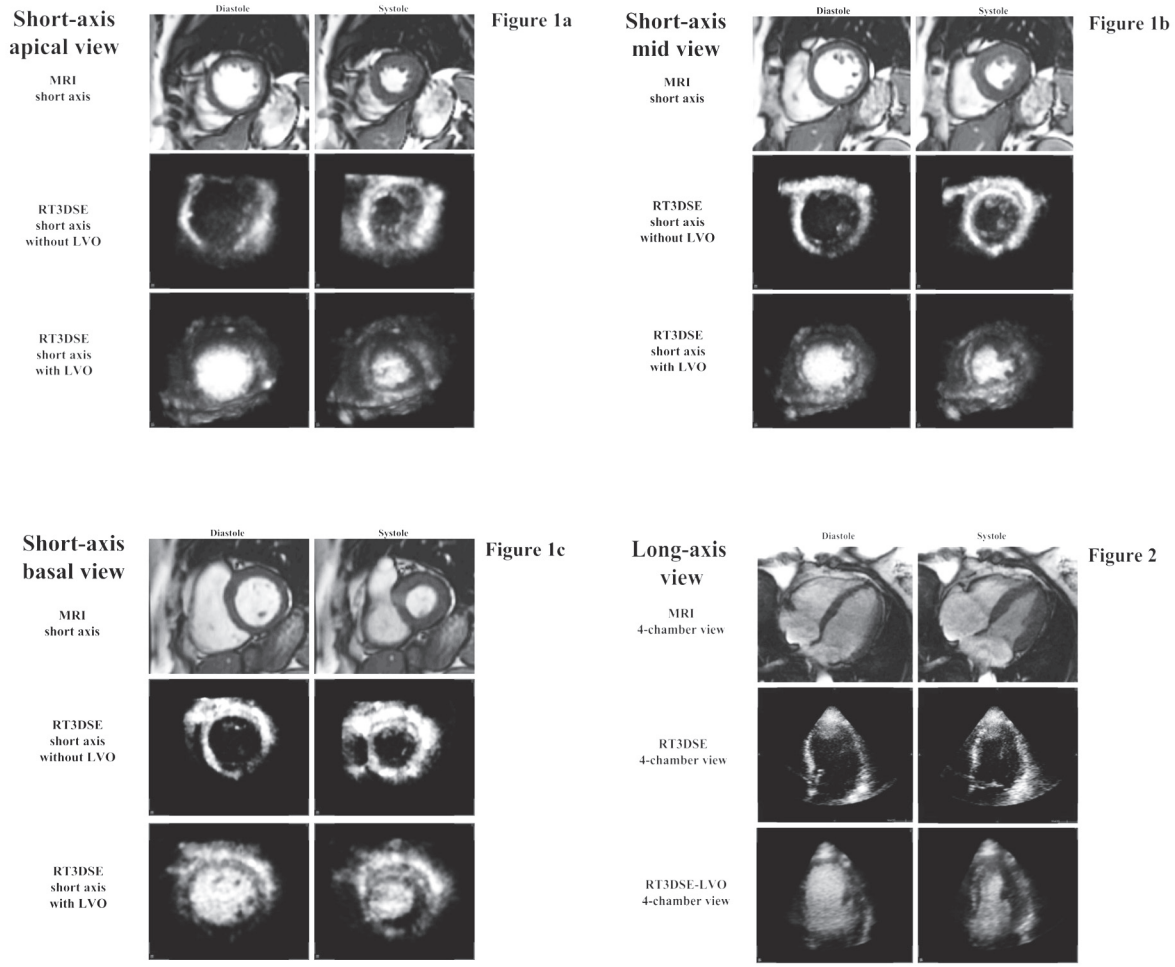
Introduction

Two-dimensional stress echocardiography (DSE) has become a well-established stress modality for the detection of coronary artery disease (CAD) (1). However, the number of left ventricular cross sections and in particular variable image quality may limit this imaging modality. Magnetic resonance imaging (MRI) overcomes these limitations and in stress MRI studies superior results with respect to the diagnosis of CAD were reported (2). More recently, the diagnostic accuracy of DSE has been improved by new developments such as second harmonic imaging (3), contrast imaging (4) and three-dimensional imaging (5). The optimal DSE test may include the use of all these new techniques in combination. In this case report we show the imaging potentials of dobutamine stress real-time three-dimensional contrast-enhanced echocardiography (RT3DE), simulating a stress MRI study with respect to unlimited left ventricular cross sections and image quality.

Case study

A 65 year-old-woman was admitted to our outpatient clinic for pre-operative risk stratification (infected knee prosthesis). Since several years she experienced stable angina. Risk factors for coronary artery disease were negative. Because of her complains and orthopedic problems (that precluded an exercise test) dobutamine stress MRI was performed. During dobutamine stress (40 μg/kg/min) the heart rate increased from 75 to 125 bpm (target heart rate was 115 bpm) and blood pressure increased from 120/75 to 125/65 mm Hg. The patient did not experience angina nor were electrocardiographic signs of myocardial ischemia seen. Routine 4-chamber, 2-chamber and 3-chamber views and basal, mid and apical short axes were recorded at rest, low-dose and peak stress. To show the capabilities of stress RT3DE, this study was performed several weeks apart from the stress MRI study with a Sonos 7500 ultrasound system (Philips, Best, The Netherlands) attached to a phased-array scanner and repeated SonoVue® boluses of

0.5 ml. During stress RT3DE similar hemodynamic data were achieved (stress heart rate 123 bpm). As seen in Figures 1-2, identical left ventricular cross sections (short-axis views at basal, mid and apical level and long-axis views) could be cropped out of the thee-dimensional data set.



Figures 1 and 2 Identical left ventricular cross sections (short-axis views at basal, mid and apical level) and apical 4-chamber views by stress MRI and RT3DSE with and without LVO

Discussion

During stress RT3DE it takes only 7 cardiac cycles (3 to 5 seconds at peak stress) to record a full three-dimensional data set. Subsequently, an unlimited number of left ventricular cross-sections can be cropped out of this data set. Contrast-enhanced images have been shown to

improve left ventricular endocardial border detection and to increase the diagnostic accuracy of conventional DSE (4). In our experience echo contrast is mandatory in most stress RT3DE studies because image quality is somewhat lower compared to conventional two-dimensional imaging (because of lower resolution and frame rate) (6). Eventually, contrast-enhanced stress RT3DE may become a competitor for stress MRI allowing fast acquisition and an unlimited number of left ventricular cross-sections. However, at this moment adequate imaging with stress RT3DE is only possible in the minority of cardiac patients. Although stress MRI may be limited by local availability and not all patients can undergo this test due to claustrophobia (in approximately 5% of patients) or contraindications such as non-compatible biometallic implants and pacemakers or implanted cardiac defibrillators, stress MRI should be considered the gold standard test to induce and visualize myocardial ischaemia (7,8). Stress MRI is well suited for overcoming the limitations of DSE. It has no acoustic window limitations and thus can comprehensively visualize the left ventricular myocardium regardless of body habitus.

References

1. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997:30:595-606.
2. Nagel E, Lehmkuhl HB, Bocksch W, Klein C, Vogel U, Frantz E, et al. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. Circulation 1999:99:763-770.
3. Sozzi FB, Poldermans D, Bax JJ, Boersma E, Vletter WB, Elhendy A, et al. Second harmonic imaging improves sensitivity of dobutamine stress echocardiography for the diagnosis of coronary artery disease. Am Heart J 2001:142:153-159.
4. Tsutsui JM, Elhendy A, Xie F, O`Leary EL, McGrain AC, Porter TR. Safety of dobutamine stress real-time myocardial contrast echocardiography. J Am Coll Cardiol 2005:19:1235-1242.
5. 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 2005:26:1625-1632.

6. Nemes A, Geleijnse ML, Krenning BJ, Soliman OII, Anwar AM, Vletter WB, et al. Usefulness of Ultrasound Contrast Agent to Improve Image Quality During Real-Time Three-Dimensional Stress Echocardiography. Am J Cardiol 2007;99:275-278
7. Paetsch I, Jahnke C, Fleck E, Nagel E. Current clinical applications of stress wall motion analysis with cardiac magnetic resonance imaging. Eur J Echocardiogr. 2005;6:317-326.
8. Mandapaka S, Hundley WG. Dobutamine cardiovascular magnetic resonance: a review. J Magn Reson Imaging. 2006;24:499-512.

Part B

Aortic stiffness measurements by echocardiography

CHAPTER 9

Increased Aortic Stiffness in Glycogenosis Type 2 (Pompe's Disease)

Int J Cardiol (in press)

Attila Nemes

Osama I.I. Soliman

Marcel L. Geleijnse

Ashraf M. Anwar

Nadine A.M.E. van der Beek

Pieter A. van Doorn

Henriette Gavallér

Éva Csajbók

Folkert J. ten Cate

Abstract

Background. Pompe's disease, also known as acid maltase deficiency or glycogen storage disease type II, is an autosomal recessive disorder in which deficient activity of the enzyme acid α-glucosidase causes intra-lysosomal accumulation of glycogen in muscle and other tissues. The current study was designed to assess aortic stiffness index (β), as a characteristic of aortic elasticity during transthoracic echocardiography in patients with Pompe`s disease.

Methods. A total of 17 patients (age 44 ± 8 years, 5 males) with Pompe`s disease were studied. Their results were compared to 17 age- and gender-matched controls. In all patients, the ascending aorta was recorded with M-mode echocardiography. β was calculated as ln(SBP/DBP)/[(SD-DD)/DD], where SBP and DBP are the systolic and diastolic blood pressures, SD and DD are the systolic and diastolic aortic diameters, and 'ln' is the natural logarithm.

Results. Diastolic aortic diameter was 27.4 ± 2.4 mm in Pompe patients and 25.6 ± 2.7 mm in controls ($P < 0.05$). Systolic aortic diameters did not differ between the groups (29.4 ± 2.5 mm vs 28.3 ± 2.4 mm, P=ns). Aortic stiffness index (β) was increased in Pompe patients compared to controls (14.6 ± 10.1 vs 5.1 ± 2.6, $P < 0.001$).

Conclusions. The results of this study indicate that aortic stiffness is increased in patients with Pompe`s diasease. This may be due to glycogen storage in the vessel wall causing reduced vascular elasticity.

Introduction

Pompe's disease, also known as acid maltase deficiency or glycogen storage disease type 2, is an autosomal recessive disorder in which deficient activity of the enzyme acid α-glucosidase causes intra-lysosomal accumulation of glycogen in muscle and other tissues (1). Muscle weakness is the most important clinical symptom, but the effect of Pompe`s disease on human aortic compliance is not well established (2). The manifestation and physiologic implications of aortic pulsatility are of considerable interest, because it provides useful information regarding aortic vasomotion function. Ascending aortic diameter changes during the heart cycle can be reliably measured with two-dimensional transthoracic echocardiography. For characterisation of aortic elasticity, aortic stiffness index (β) can be used (3). The current study was designed to assess ascending aortic elastic properties in patients with Pompe`s disease and to compare these results to age- and gender-matched controls.

Materials and methods

Study population. A total of 17 patients with typical features of adult-onset Pompe`s disease (44 ± 8 years, 5 males) without cardiovascular risk factors (diabetes mellitus, hypertension, smoking, hypercholesterolaemia) were investigated. Pompe diagnosis was based on clinical symptoms (exercise intolerance due to skeletal muscle problem) caused by partial deficiency of acid α-glucosidase activity. Their results were compared to 17 age- and gender-matched controls without cardiovascular risk factors. None of the patients or control subjects received therapeutic drugs. Informed consent was obtained from each patient and the study was approved by the institutional review board.

Blood pressure measurement. Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured in the supine position with an automatic mercury cuff sphygmomanometer from the left arm after 10 min of rest. None of the patients or control subjects used coffee or tea within one hour before blood pressure measurements and by exclusion none of the patients or control subjects were smoker.

Transthoracic echocardiography. All subjects underwent a complete two-dimensional transthoracic echocardiography and Doppler study using a Philips Sonos 7500 echocardiography equipment (Philips, Best, The Netherlands) in the left lateral decubitus position from multiple windows. Systolic and diastolic ascending aortic diameters (SD and DD, respectively) were recorded in M-mode at a level of 3 cm above the aortic valve from a parasternal long-axis view (Figure 1). The SD and DD were measured at the time out of maximum aortic anterior motion and at the peak of QRS complex, respectively. Aortic stiffness index (β) was defined as ln(SBP/DBP)/[(SD-DD)/DD], where 'ln' is the natural logarithm.

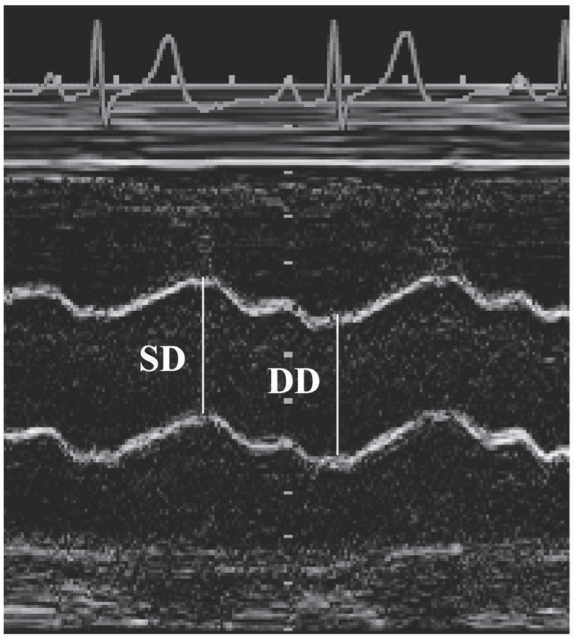


Figure 1 Measurements of systolic (SD) and diastolic (DD) diameters of the ascending aorta are shown on the M-mode tracing obtained at a level 3 cm above the aortic valve.

Statistical analysis. All data are reported as mean ± standard deviation. For comparing variables, the student t test was used (SPSS 12.0 software). A value of $p<0.05$ was considered statistically significant.

Reproducibility of echocardiographic measurements. The reproducibility of the aortic diameter measurements was assessed in all 17 Pompe patients at both systole and diastole by two independent, blinded observers. Agreement between the two observers was verified using the Bland-Altman method (4).

Results

Transthoracic echocardiography. All patients had normal left atrial and left ventricular dimensions and function. Mean diastolic aortic diameter was larger and mean aortic stiffness index (β) was significantly increased in Pompe`s disease patients compared to controls (Table 1). Individual β indices of Pompe patients and control subjects are presented in Figure 2.

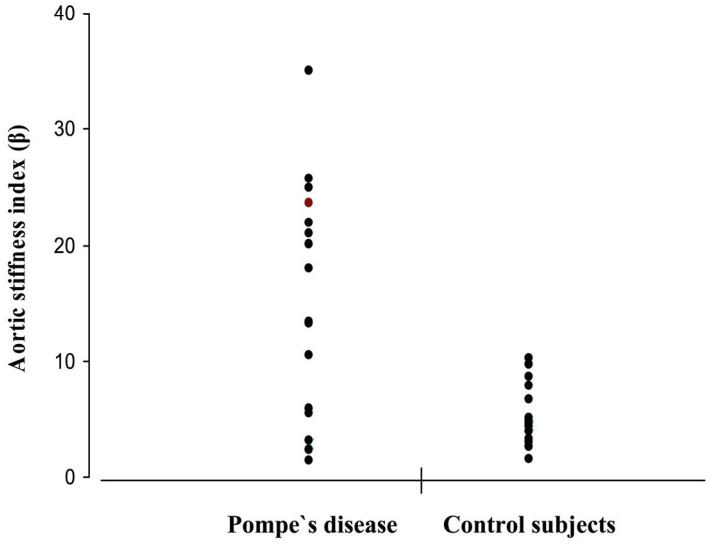


Figure 2 Individual β indices of Pompe patients and control subjects

Table 1 Echocardiographic and blood pressure data in Pompe patients and normal subjects

	Group 1 (normal subjects)	Group 2 (Pompe`s disease)
Body mass index (kg/m^2)	30.3 ± 5.7	23.9 ± 2.7 #
LV end-diastolic diameter (mm)	49.5 ± 6.7	48.1 ± 3.9
LV end-systolic diameter (mm)	31.1 ± 8.5	31.3 ± 4.8
LV ejection fraction (%)	68.9 ± 7.7	69.7 ± 6.9
Systolic aortic diameter (mm)	28.3 ± 2.4	29.4 ± 2.5
Diastolic aortic diameter (mm)	25.6 ± 2.7	27.4 ± 2.4 *
Pulsatile change in aortic diameter (mm)	2.9 ± 1.3	2.0 ± 2.0
Systolic blood pressure (mm Hg)	132.6 ± 9.4	134.2 ± 15.4
Diastolic blood pressure (mm Hg)	83.5 ± 8.6	80.5 ± 9.8
Aortic pulse pressure (mm Hg)	49.1 ± 9.6	53.6 ± 12.1
Aortic stiffness index (β)	5.1 ± 2.6	14.6 ± 10.1 #

Continuous variables are given as mean ± standard deviation * = P <0.05. # = P <0.001.
LV = left ventricular.

Reproducibility. The mean ± SD difference in values obtained by two observers for the measurements of systolic aortic diameter was 0.7 ± 1.2 mm, with a correlation coefficient between these independent measurements of 0.84 (P <0.001). At diastole, the difference between these observations was 0.2 ± 1.4 mm, with a correlation coefficient between observations of 0.88 (P <0.001). The interobserver difference in values was within twofold of the standard deviation of the mean (Figure 3).

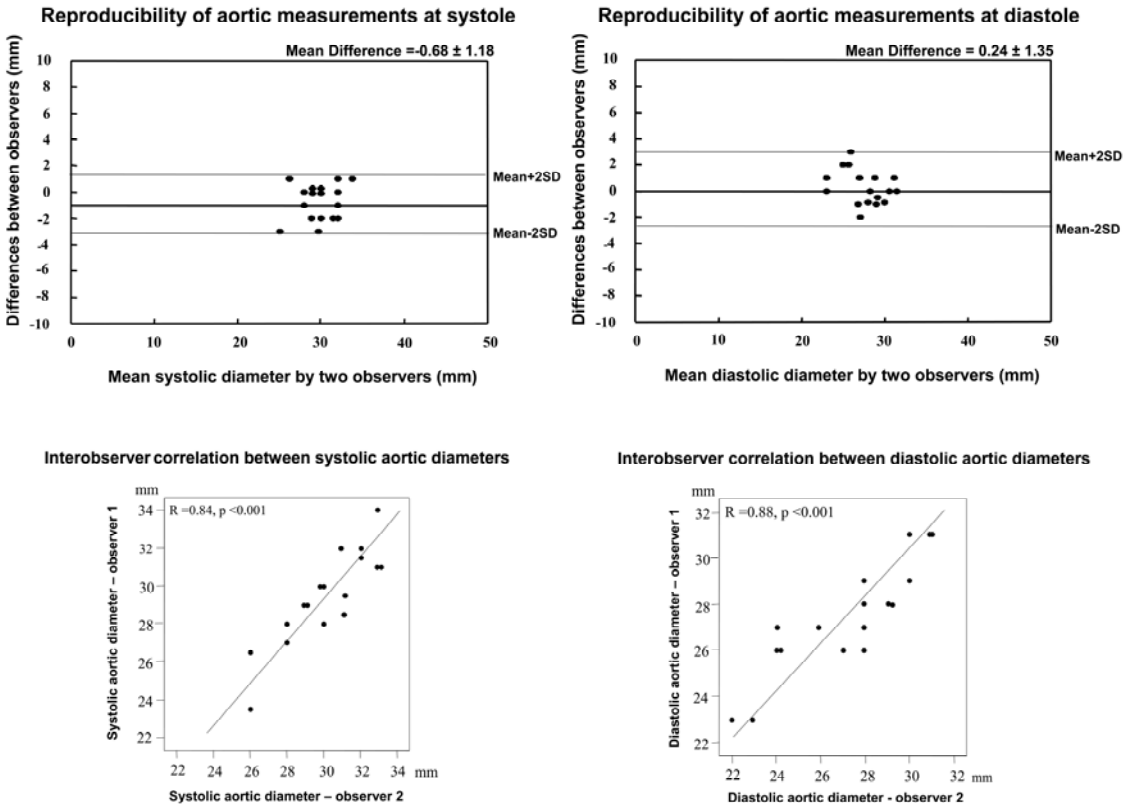


Figure 3 Interobserver correlations and reproducibility measurements between systolic and diastolic aortic diameters in Pompe`s patients.

Discussion

Pompe`s disease is an autosomal recessive lysosomal storage disorder, caused by acid α-glucosidase deficiency (5). To the best of the authors` knowledge, the elastic properties of the aorta have never been reported in Pompe patients. Greater diastolic aortic diameters with smaller pulsatile aortic diameter changes related to aortic remodelling resulted in increased β values in Pompe patients.

Increased arterial stiffness is an independent risk factor and predictor of cardiovascular mortality in a variety of diseases (6). Direct measurement of arterial stiffness requires invasive techniques unsuitable for routine clinical practice (3). In the present study, the aortic elastic parameters were derived from the pulsatile change in ascending aortic diameter and conventional left brachial arterial systolic and diastolic blood pressures. Aortic stiffness index

(β), a characteristic of aortic elasticity, represents the slope of the exponential function relating the relative arterial pressure and the distention ratio of the artery and characterizes the entire deformation behavior of the vascular wall. This non-invasive β index has been confirmed as a determinant of aortic distensibility, with a high degree of accuracy in comparison with invasive methods (3).

In recent morphological studies in Pompe patients glycogen storage has been demonstrated in smooth muscle cells of the arteries and veins (7). With disease progression, the integrity of the blood vessel wall may become lost, which can explain the occurrence of aneurysms in the basal arteries in Pompe`s disease (7,8). It can only be hypothesized that glycogen storage is responsible for the increased aortic stiffness in our study. Other factors known to be associated with aortic stiffness such as diabetes mellitus, hypertension, smoking or hypercholesterolaemia were excluded in our patients. At this moment, α-glucosidase enzyme replacement therapy is under investigation in the multicenter LOTS (Late Onset Therapy Study) trial. If aortic stiffness will improve with enzyme replacement therapy, this may confirm the potential role of glycogen storage in the development of increased aortic stiffness. The most important limitation is that noninvasive brachial cuff pressure measurement instead of a direct assessment of blood pressure by a catheter was used. However, others have shown excellent correlation in the evaluation of aortic distensibility using invasive and noninvasive methods (3).

Conclusions. Aortic elastic properties are altered and aortic distensibility is decreased in patients with Pompe`s disease. These alterations may be due to glycogen storage in the aortic wall. Potential reversal of aortic distensibility should be tested in ongoing enzyme replacement therapy trials.

References

1. Hagemans ML, Winkel LP, Van Doorn PA, Hop WJ, Loonen MC, Reuser AJ, et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. Brain 2005;128:671-677.
2. Engel AG, Gomez MR, Seybold ME, Lambert EH. The spectrum and diagnosis of acid maltase deficiency. Neurology 1973;23:95-106.
3. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. Eur Heart J 1990;11:990-996.
4. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-310.
5. Hirschhorn R RA. Glycogen storage disease type II; acid a-glucosidase (acid-maltase) deficiency. In: Scriver CR BA, Valle D, Sly WS, editors, editor. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill; 2000. p. 3389-3420.
6. Gosling RG, Budge MM. Terminology for describing the elastic behavior of arteries. Hypertension 2003;41:1180-1182.
7. Winkel LP, Kamphoven JH, van den Hout HJ, Severijnen LA, van Doorn PA, Reuser AJ, et al. Morphological changes in muscle tissue of patients with infantile Pompe's disease receiving enzyme replacement therapy. Muscle Nerve 2003;27:743-751.
8. Braunsdorf WE. Fusiform aneurysm of basilar artery and ectatic internal carotid arteries associated with glycogenosis type 2 (Pompe's disease). Neurosurgery 1987;21:748-749.

CHAPTER 10

Mucopolysaccharidosis Type I (Scheie Syndrome) is Associated with Increased Ascending Aortic Stiffness

submitted

Attila Nemes

Remco G.M. Timmermans

Marcel L. Geleijnse

J.H. Paul Wilson

Osama I.I. Soliman

Boudewijn J. Krenning

Folkert J. ten Cate

Abstract

Objective. Mucopolysaccharidosis type I (MPS IS) is a rare autosomal recessive disease caused by a deficiency of the lysosomal enzyme α-L-iduronidase, which is involved in the degradation of sulfated glycosaminoglycans (GAGs). The deficiency results in the intra- and pericellular accumulation of the GAGs heparin sulfate and dermatan sulfate.

Methods. Eight adult patients with typical features of MPS IS were included and compared to age and gender-matched controls. With transthoracic echocardiography, cyclic ascending aortic diameter changes and the aortic stiffness index was measured to characterize aortic elasticity.

Results. In MPS IS patients, systolic and diastolic aortic diameters and mean aortic stiffness index were significantly increased compared to age and sex matched controls.

Conclusions. The results of the present study demonstrate that in addition to the known cardiac complications, MPS IS patients have an impairment of aortic elasticity. Further follow-up studies are needed to examine arterial elasticity using other methods in this patient population, and to detect possible effects of enzyme replacement therapy.

Introduction

Mucopolysaccharidosis type I (MPS I) is a rare autosomal recessive disease caused by deficiency of the lysosomal enzyme α-L-iduronidase. This enzyme is involved in the degradation of sulfated glycosaminoglycans (GAG)s and deficiency results in intracellular and pericellular accumulations of the GAGs heparin sulfate and dermatan sulphate (1). Deficiency of α-L-iduronidase gives rise to three main clinical entities – Hurler syndrome (MPS IH), presenting in infancy and the most severe phenotype, Hurler-Scheie syndrome (MPS IH/S), a phenotype presenting in childhood and of intermediate severity, and Scheie syndrome (MPS IS), the mildest form of MPS I. Cardiomyopathy and thickening of cardiac valves and large vessels have been described in MPS I patients, especially in MPS IH (2,3). Autopsy studies have described aortic GAG accumulations in MPS IH patients. GAG accumulation in the aorta could conceivably affect aortic wall function and contribute to further decay in cardiac function (4). With transthoracic echocardiography, cyclic ascending aortic diameter changes and the aortic stiffness index (β) can be measured to characterize aortic elasticity (5). The current study was designed to assess ascending aortic stiffness in adult patients with the less severe MPS IS phenotype.

Materials and methods

Eight adult patients with typical features of MPS IS aged 30 ± 6 years (five men) were included (Table 1). The diagnosis of MPS I was based on demonstrating a deficiency of α-L-iduronidase activity in cultured fibroblasts. The results of the ultrasound studies were compared to 20 age- and gender-matched healthy controls. Informed consent was obtained from each patient and the study was approved by the institutional review board. In all patients blood pressure was measured in the supine position with a mercury sphygmomanometer. None of the patients or control subjects received therapeutic drugs, used coffee or tea within one hour

before blood pressure measurements or was a smoker. All subjects underwent a complete 2-dimensional transthoracic echocardiographic and Doppler study using a Philips Sonos 7500 system (Philips, Best, The Netherlands) in the left lateral decubitus position from multiple windows. Systolic and diastolic ascending aortic diameters (SD and DD, respectively) were recorded in M-mode at a level 3 cm above the aortic valve from a parasternal long-axis view, according to a method described previously in more detail (5,6). SD and DD were measured at the time of maximum aortic anterior motion and at the peak of the QRS complex, respectively. The aortic stiffness index was calculated from the echocardiographically derived aortic diameters and the clinical blood pressure by using the following formula ln(SBP/DBP)/[(SD-DD)/DD], where 'ln' is the natural logarithm. All data are reported as mean ± standard deviation. For comparing variables, the student *t* test was used (SPSS 12.0 software). A value of $p<0.05$ was considered to be statistically significant. Interobserver reproducibility for measuring systolic and diastolic aortic diameters in our institution is 84 and 88%, respectively (7).

Results

Clinical and demographic data of MPS IS patients and controls are presented in Table 1. Systolic and diastolic aortic diameters of MPS IS patients were significantly increased. Mean aortic stiffness index (β) was significantly increased in MPS I patients compared to controls (Figure 1).

Table 1 Echocardiographic and blood pressure data in MPS I patients and normal subjects

	Group 1 (normal subjects)	Group 2 (patients with MPS I)
LV end-diastolic diameter (mm)	46.6 ± 4.6	47.3 ± 3.5
LV end-systolic diameter (mm)	28.1 ± 2.8	31.4 ± 4.0#
LV ejection fraction (%)	70.9 ± 5.9	64.9 ± 4.6#
Systolic aortic diameter (mm)	25.7 ± 2.7	28.1 ± 3.3#
Diastolic aortic diameter (mm)	22.4 ± 2.6	27.4 ± 3.2*
Pulsatile change in aortic diameter (mm)	3.3 ± 1.2	0.8 ± 0.4*
Systolic blood pressure (mm Hg)	129.6 ± 24.2	115.3 ± 20.7
Diastolic blood pressure (mm Hg)	77.3 ± 13.2	67.3 ± 9.8
Aortic pulse pressure (mm Hg)	52.3 ± 16.2	48.0 ± 14.6
Aortic stiffness index (β)	3.9 ± 1.5	23.1 ± 10.4*

Continuous variables are given as mean ± standard deviation * P <0.001. # P<0.05

LV = left ventricular.

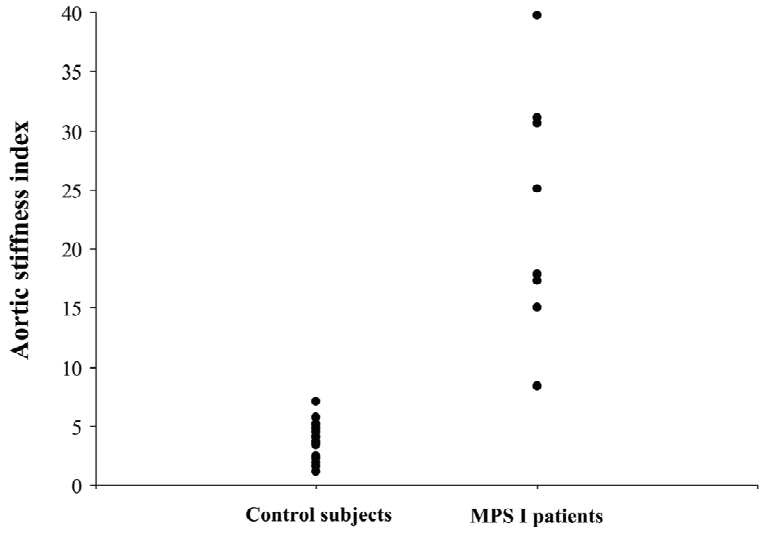


Figure 1 Individual β indices of MPS I patients and control subjects

Discussion

To the best of the authors' knowledge this is the first time that alterations in aortic elasticity are investigated by a non-invasive echocardiographic method in adult patients with MPS IS. Direct measurement of arterial stiffness requires invasive techniques unsuitable for routine clinical practice. Stefanadis *et al.* have demonstrated that the non-invasively evaluated β index as a determinant of aortic distensibility is comparable with invasive methods with a high degree of accuracy (5).

Increased aortic stiffness in MPS IS patients was found as compared to age- and gender-matched healthy controls. MPS I is a rare disease in which a deficiency of the lysosomal enzyme α-L-iduronidase results in accumulation of heparan sulfate and dermatan sulfate within the central nervous system, lungs, liver, bones, cartilage and heart. The disorder is clinically heterogeneous, the clinical spectrum ranging from the very severe Hurler syndrome to the attenuated Scheie syndrome, with a diverse group of intermediate severity known as Hurler-Scheie.

Within the heart, GAG accumulation is associated with thickened cardiac valves, progressive narrowing and occlusion of the epicardial coronary arteries, and congestive heart failure. A variety of vessels can be involved showing various facets of the arteriopathy in MPS I. The assessment of coronary artery involvement in MPS I is difficult. Because of its diffuse nature, routine coronary angiography fails to identify severe myointimal proliferation (8). Irregular narrowing of the abdominal aorta with either multiple asymmetric wall lesions or abrupt concentric narrowing has been found to be present in some children by different imaging methods (aortography, sonography or magnetic resonance imaging) (9). In accordance with a recently published study, the aorta in our MPS I patients was dilated suggesting remodeling of this vessel (2). In addition to these changes in aortic dimensions, elastic properties were also changed and may also be due to GAG storage in the aortic wall. In MPS

IH, the accumulation of dermatan sulfate has been shown to impair the formation of normal elastin fibres by inactivating the chaperone involved, elastin-binding protein (10,11). Apart from the abnormal elastin structure, changes in collagen formation and collagen cross-linking have been described in other tissues such as skin and cornea. Such changes in collagen could contribute to the functional changes in the aorta and other blood vessels (12,13).

Enzyme replacement therapy with recombinant human α-L-iduronidase (laronidase, Aldurazyme, BioMarin Pharmaceutical Inc., Novato, California, and Genzyme Corporation, Cambridge, Massachusetts) has recently been approved for use in children with MPS I (14). Preliminary results by Braunlin *et al.* suggest that long-term enzyme replacement therapy is beneficial for the myocardium, but the cardiac valves appeared unresponsive. Unfortunately, effects on blood vessels was not studied (3).

In conclusion, this study provides evidence that aortic involvement, which has previously only been described in post mortem studies in severe form MPS IH, also occurs in the milder forms of MPS I, like MPS IS. The measurement of aortic stiffness by a non-invasive means provides a way to follow progression of disease and the effect of new treatment options. The potential reversibility of this impaired aortic distensibility should be examined in ongoing enzyme replacement therapy trials.

References

1. Neufeld E, Muenzer J. The mucopolysaccharidoses. In: Scriver CR BA, Valle D, Sly WS, editor. The Metabolic and Molecular Bases of Inherited Diseases. New York: McGraw-Hill; 2001. p. 3421-3452.
2. Braunlin E, Mackey-Bojack S, Panoskaltsis-Mortari A, Berry JM, McElmurry RT, Riddle M, et al. Cardiac functional and histopathologic findings in humans and mice with mucopolysaccharidosis type I: implications for assessment of therapeutic interventions in hurler syndrome. Pediatr Res 2006;59:27-32.
3. Braunlin EA, Berry JM, Whitley CB. Cardiac findings after enzyme replacement therapy for mucopolysaccharidosis type I. Am J Cardiol 2006;98:416-418.
4. Renteria VG, Ferrans VJ, Roberts WC. The heart in the Hurler syndrome: gross, histologic and ultrastructural observations in five necropsy cases. Am J Cardiol 1976;38:487-501.
5. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. Eur Heart J 1990;11:990-996.
6. Stefanadis C, Dernellis J, Tsiamis E, Stratos C, Diamantopoulos L, Michaelides A, et al. Aortic stiffness as a risk factor for recurrent acute coronary events in patients with ischaemic heart disease. Eur Heart J 2000;21:390-396.
7. Nemes A, Soliman OII, Geleijnse ML, Anwar AM, van der Beek NAME, van Doorn PA, et al. Increased aortic stiffness in glycogenosis type 2 (Pompe`s disease). Int J Cardiol (in press).
8. Braunlin EA, Hunter DW, Krivit W, Burke BA, Hesslein PS, Porter PT, et al. Evaluation of coronary artery disease in the Hurler syndrome by angiography. Am J Cardiol 1992;69:1487-1489.
9. Taylor DB, Blaser SI, Burrows PE, Stringer DA, Clarke JT, Thorner P. Arteriopathy and coarctation of the abdominal aorta in children with mucopolysaccharidosis: imaging findings. AJR Am J Roentgenol 1991;157:819-823.
10. Hinek A, Wilson SE. Impaired elastogenesis in Hurler disease: dermatan sulfate accumulation linked to deficiency in elastin-binding protein and elastic fiber assembly. Am J Pathol 2000;156:925-938.
11. Hinek A, Braun KR, Liu K, Wang Y, Wight TN. Retrovirally mediated overexpression of versican v3 reverses impaired elastogenesis and heightened proliferation exhibited by fibroblasts from Costello syndrome and Hurler disease patients. Am J Pathol 2004;164:119-131.
12. Holbrook KA, Byers PH. Structural abnormalities in the dermal collagen and elastic matrix from the skin of patients with inherited connective tissue disorders. J Invest Dermatol 1982;79 Suppl 1:7s-16s.
13. Rummelt V, Meyer HJ, Naumann GO. Light and electron microscopy of the cornea in systemic mucopolysaccharidosis type I-S (Scheie's syndrome). Cornea 1992;11:86-92.
14. Wraith EJ, Hopwood JJ, Fuller M, Meikle PJ, Brooks DA. Laronidase treatment of mucopolysaccharidosis I. BioDrugs 2005;19:1-7.

CHAPTER 11

Aortic Valve Replacement for Aortic Stenosis is Associated with Improved Aortic Distensibility at Long-Term Follow-up

American Heart Journal 2007; 153: 147-151

Attila Nemes

Tjebbe W. Galema

Marcel L. Geleijnse

Osama I.I. Soliman

Sing-Chien Yap

Ashraf M. Anwar

Folkert J. ten Cate

Abstract

Background. Aortic valve stenosis (AS) is the most frequent form of valvular heart disease. The number of studies evaluating the effect of aortic valve replacement (AVR) for AS on aortic vascular function is limited. The aim of the present study was to examine alterations in aortic distensibility in AS patients during a one-year follow-up after AVR.

Methods. Twelve patients with severe AS who underwent AVR were prospectively investigated (mean age 65 ± 11 years, 7 males). Systolic and diastolic ascending aortic diameters (SD and DD, respectively) were recorded in M-mode 3 cm above the aortic valve from a parasternal long-axis view. The SD and DD were measured at the time of maximum anterior motion of the aorta and at the start of the QRS complex, respectively. Aortic stiffness index (β) was defined as $[\ln(SBP/DBP)]\times DD/\Delta D$, where 'ln' is the natural logarithm, SBP and DBP are the systolic and diastolic blood pressure values and $\Delta D = SD–DD$.

Results. As expected, aortic stenosis severity and left ventricular mass decreased significantly after AVR. Aortic diameter changes (systolic minus diastolic dimensions) progressively increased, and the aortic stiffness index progressively improved to levels comparable to age, gender and risk factor-matched controls at the one year assessment.

Conclusions. AVR in AS patients is associated with a progressive improvement in aortic distensibility to one year values similar to age, gender and risk factor-matched controls.

Introduction

Aortic valve stenosis (AS) is the most frequent form of valvular heart disease. Impaired coronary microcirculation and decreased coronary flow reserve (CFR) are well-known alterations associated with AS regardless of the presence or absence of coronary artery disease (CAD) (1) In recent studies, improvement in CFR has been described within one-year after AVR (2,3). Impaired aortic elastic properties have also been demonstrated in AS patients (4,5). This finding supported the suggestion that decreased aortic distensibility in valvular AS can be an early manifestation of the atherosclerotic process (endothelial dysfunction), decreased perfusion of the aorta or other factors beyond physical pressure effects (4). Unfortunately, long-term data on changes in aortic elasticity after AVR are not yet available. The aim of the present study was to examine alterations in aortic distensibility in AS patients during an one-year follow-up after AVR.

Methods

Study population. Twelve patients with severe AS who underwent AVR were prospectively investigated (mean age 65 ± 11 years, 7 males). Risk factors for cardiovascular disease included hypertension in two and diabetes in one. AVR was carried on in all patients, four patients with coronary artery disease underwent additional coronary artery bypass grafting. All results were compared to 12 age-, gender- and risk factor-matched controls. All patients underwent transthoracic two-dimensional echocardiography before and 3-weeks, 6-months and 12-months after AVR. Informed consent was obtained from each patient and the study was approved by the hospital`s medical ethical committee and complied with the Declaration of Helsinki.

Blood pressure measurement. Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured in the supine position with an automatic mercury cuff sphygmomanometer from the left arm after 10 min of rest. Regarding to the European Guidelines for the Management of Hypertension (2003) blood pressure values were used as reference phase I (appearance of a tone) and phase V (disappearance) of Korotkoff sounds to identify SBP and DBP, respectively (6). Blood pressure values were averaged from three consecutive measurements. None of the patients used coffee or tea within one hour before blood pressure measurements.

Transthoracic echocardiography. All patients underwent a complete two-dimensional echocardiography and Doppler study using a Philips Sonos 7500 system (Philips, Best, The Netherlands) in the left lateral decubitus position from multiple windows. Systolic and diastolic ascending aortic diameters (SD and DD, respectively) were recorded in M-mode at a level of 3 cm above the aortic valve from a parasternal long-axis view (Figure 1).

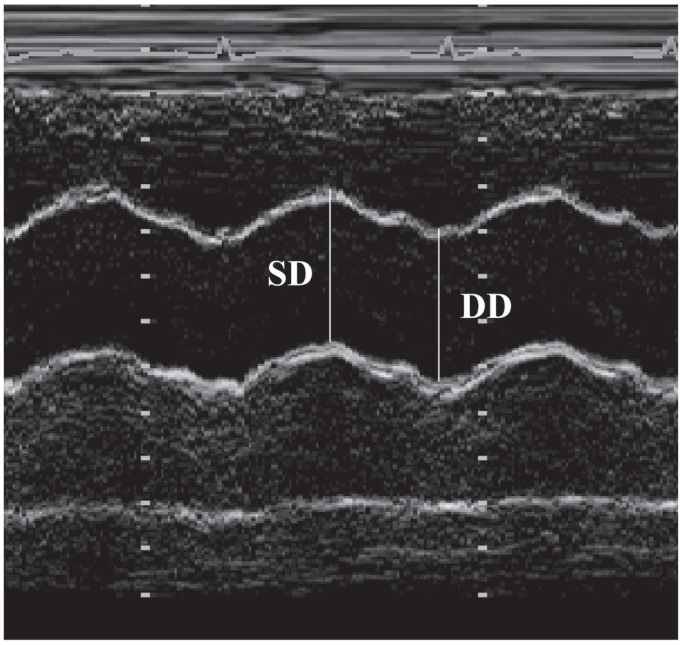


Figure 1 Measurements of systolic (SD) and diastolic (DD) diameters of the ascending aorta are shown on the M-mode tracing obtained at a level 3 cm above the aortic valve.

Gain, depth, and sector angles were individualized for the best measurement. The SD and DD were measured at the time of maximum anterior motion of the aorta and at the start of the QRS complex, respectively. Aortic stiffness index (β) was defined as [ln(SBP/DBP)]×DD/ΔD, where 'ln' is the natural logarithm and ΔD = SD – DD (7).

Statistical analysis. Data are reported as means ± standard deviation. For comparison between variables, analysis of variance (ANOVA) test with Bonferroni adjustment was used. A value of $p < 0.05$ was considered statistically significant. SPSS 12.0 software was used for statistical calculations. The reproducibility of the aortic diameter measurements was tested in all AS patients at both systole and diastole by two blinded observers. Agreement between the two observers was verified using the Bland-Altman method (8).

Results

Cardiovascular changes after AVR. All echocardiographic, haemodynamic and aortic data are presented in the Table. Post-AVR a significant and sustained decrease was found in peak and mean aortic gradients. Left ventricular mass progressively decreased, aortic diameter changes (systolic minus diastolic dimensions) progressively increased, and the aortic stiffness index progressively improved to levels comparable to age, gender and risk factor-matched controls at the one year assessment.

Table 1. Clinical and echocardiographic characteristics of the study population

	Controls	Before AVR	3 weeks after AVR	6 months after AVR	12 months after AVR
Echocardiographic data					
End-diastolic LV diameter (mm)	50.6 ± 4.2$^{\&\$}$	50.3 ± 16.4	44.9 ± 5.9	44.2 ± 3.6	45.1 ± 5.5
End-systolic LV diameter (mm)	32.0 ± 4.0	30.0 ± 6.8	28.4 ± 9.5	27.8 ± 3.5	29.0 ± 4.9
Interventricular thickness (mm)	10.3 ± 1.1$^{*\&}$	15.0 ± 4.6	14.1 ± 3.6	13.4 ± 2.4	13.1 ± 3.3
Posterior wall thickness (mm)	9.8 ± 1.0$^{*\&}$	13.7 ± 3.9	12.8 ± 2.2	11.5 ± 1.8	12.0 ± 3.5
Left ventricular mass (g)	234 ± 45	397 ± 288	284 ± 100	241 ± 58	229 ± 129
Peak aortic gradient (mm Hg)	-	90.5 ± 24.3	18.5 ± 7.3*	15.0 ± 4.5*	18.7 ± 5.1*
Mean aortic gradient (mm Hg)	-	53.3 ± 12.9	9.3 ± 4.5*	8.4 ± 2.4*	9.3 ± 2.5*
Hemodynamic data					
Systolic BP (mm Hg)	149.8 ± 15.0$^{\&}$	144.3 ± 20.7	122.1 ± 10.3	135.8 ± 14.6	132.5 ± 22.1
Diastolic BP (mm Hg)	87.4 ± 8.8$^{\&}$	78.9 ± 9.5	73.3 ± 7.5	77.1 ± 6.6	77.5 ± 11.2
Pulse pressure (mm Hg)	62.4 ± 10.6$^{\&}$	65.3 ± 15.7	48.8 ± 10.5	58.8 ± 10.3	55.0 ± 13.3
Ascending aortic data					
Aortic SD (mm)	30.6 ± 3.8	30.7 ± 4.7	29.4 ± 2.9	31.0 ± 3.3	31.0 ± 4.2
Aortic DD (mm)	27.9 ± 3.0	29.6 ± 4.6	28.3 ± 2.9	29.3 ± 3.2	29.0 ± 4.1
Aortic SD - DD (mm)	2.3 ± 1.1$^{*\&}$	1.1 ± 0.5	1.1 ± 0.6	1.7 ± 0.9	2.1 ± 0.8*
Aortic stiffness index (β)	8.2 ± 4.5$^{*\&}$	19.6 ± 10.8	16.7 ± 7.5	12.5 ± 7.1	8.4 ± 3.5*

Variables are expressed as means ± standard deviation. Abbreviation: BP, blood pressure; LV, left ventricle; DD, diastolic diameter; SD, systolic diameter.

* = P <0.05 compared to before AVR. & = P <0.05 compared to 3 weeks after AVR. $ = P <0.05 compared to 6 months after AVR.

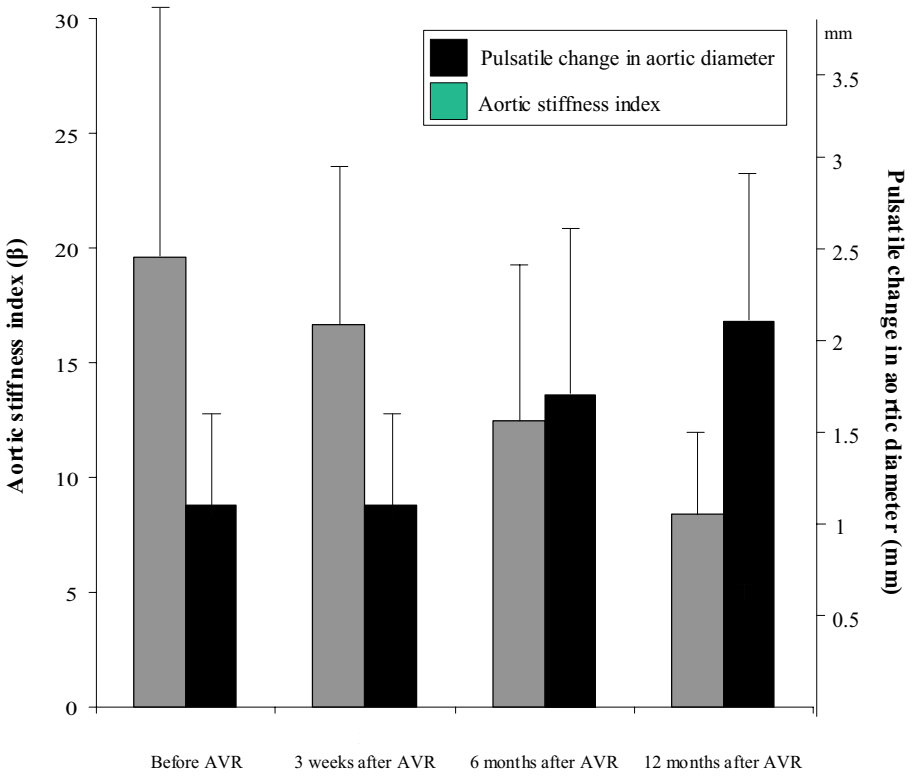


Figure 2 Aortic stiffness index and pulsatile change in aortic diameter during follow-up

Reproducibility. The mean ± standard deviation difference in values obtained by two observers for the measurements of aortic diameter at systole was –0.4 ± 1.7 mm, with a correlation coefficient between these independent measurements of 0.91 ($p < 0.001$) (Figures 3A and 4A). At diastole, the difference between these observations was – 0.02 ± 1.6 mm, with a correlation coefficient between observations of 0.91 ($p < 0.001$) (Figures 3B and 4B).

Figure 3A Interobserver correlation between systolic aortic diameter

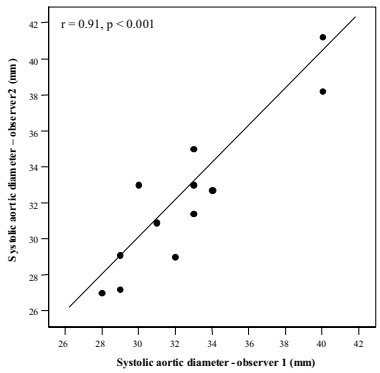


Figure 4A Reproducibility of systolic aortic measurements

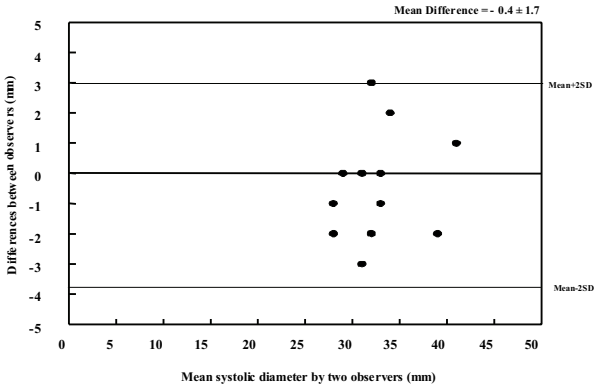


Figure 3B Interobserver correlation between diastolic aortic diameter

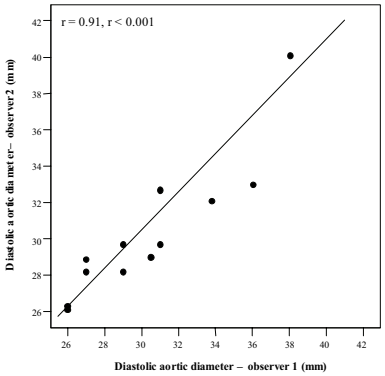


Figure 4B Reproducibility of diastolic aortic measurements

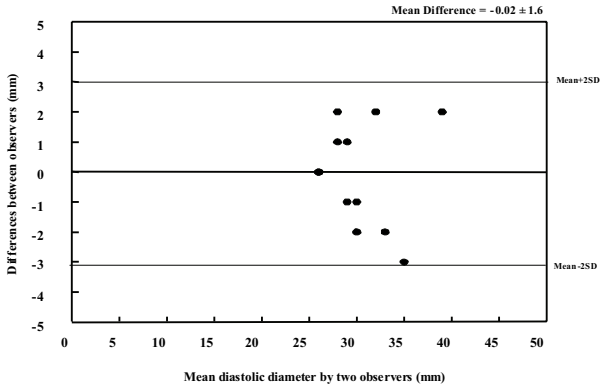


Figure 3A/B and 4A/B Interobserver correlation (r = 0.91, p <0.001 for systolic and (r = 0.91, p <0.001 for diastolic aortic diameters) and reproducibility of systolic and diastolic aortic measurements.

Discussion

The number of studies evaluating the effect of AVR for AS on aortic vascular function is limited. To the best of the authors knowledge this is the first study that examined aortic elasticity changes up to one year after AVR. In prior studies it has been shown that pulsatile changes in ascending aortic diameter can be measured during routine transthoracic echocardiography. Stefanadis *et al.* described that noninvasive measurements of aortic distensibility by echocardiography, based on aortic dimensions and blood pressure data, are as accurate as invasive methods (9). In the present study, aortic stiffness index (β) continued to

decrease up to one year after AVR corresponding to improved aortic elasticity to a level comparable to age, gender and risk factor-matched controls.

There are a limited number of studies evaluating vascular alterations in AS. In most of them, mainly the coronary microcirculation was examined (1-4,10,11). Reduced coronary flow reserve (CFR) has been demonstrated in AS patients regardless the presence or absence of coronary artery disease (CAD) (1-4,10,11). Improvement in CFR within one year after AVR for AS was described by different groups. This improvement paralleled the reduction in left ventricular hypertrophy (2).

In a previous study, we reported increased aortic stiffness in AS patients without CAD to a level comparable to that found in CAD patients without valvular heart disease (4). This underscores the hypothesis that aortic vascular alterations in AS are caused by multiple factors. Barbetseas *et al.* described that AVR with a mechanical valve resulted in a significant decrease in aortic distensibility one week after AVR (5). However, this was a transient effect, since 6 months post-operatively aortic function ameliorated. The authors explained their findings by AVR-induced transient trauma to the arterial wall, so called *`aortic root stunning`* (5). In our study, this claimed transient early period of *`aortic root stunning`* may have been missed because our first post-AVR assessment was done not earlier than three weeks after AVR. We demonstrated a progressive improvement in aortic stiffness index to levels comparable to age, gender and risk factor-matched controls at the one-year assessment. Turbulent flow across the stenotic aortic valve may damage aortic root endothelium. One of the possible explanations for improvement in vascular elasticity may be recovery of damaged aortic root endothelium, which has an important role in the production of vasorelaxant factors (12). However, pressure changes in the proximal aorta also may have played a role in this improvement.

Some studies evaluated changes in vascular function after aortic root replacement. Schmidtke *et al.* investigated the influence of different Ross procedure techniques on

distensibility of the aortic root (13). They found that the freestanding root, inclusion and subcoronary techniques resulted in comparable hemodynamics, root size and distensibility. Rajappan *et al.* demonstrated that up to one year after aortic root replacement, the wall of both the allogenic and xenogenic root retained near-normal distensibility (14). They were the first to describe a correlation between elastic properties of the aortic root and left ventricular mass.

Conclusions. AVR in AS patients is associated with progressive improvement in aortic distensibility to one year values similar to age, gender and risk factor-matched controls.

References

1. Rajappan K, Rimoldi OE, Dutka DP, Ariff B, Pennell DJ, Sheridan DJ, et al. Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries. Circulation 2002;105:470-476.
2. Hildick-Smith DJ, Shapiro LM. Coronary flow reserve improves after aortic valve replacement for aortic stenosis: an adenosine transthoracic echocardiography study. J Am Coll Cardiol 2000;36:1889-1896.
3. Nemes A, Forster T, Kovacs Z, Thury A, Ungi I, Csanady M. The effect of aortic valve replacement on coronary flow reserve in patients with a normal coronary angiogram. Herz 2002;27:780-784.
4. Nemes A, Forster T, Csanady M. Decreased aortic distensibility and coronary flow velocity reserve in patients with significant aortic valve stenosis with normal epicardial coronary arteries. J Heart Valve Dis 2004;13:567-573.
5. Barbetseas J, Alexopoulos N, Brili S, Aggeli C, Marinakis N, Vlachopoulos C, et al. Changes in aortic root function after valve replacement in patients with aortic stenosis. Int J Cardiol 2005.
6. ESH-ESC Guidelines Committee. Guidelines for the Management of Hypertension. 2003:8-9.
7. Lacombe F, Dart A, Dewar E, Jennings G, Cameron J, Laufer E. Arterial elastic properties in man: a comparison of echo-Doppler indices of aortic stiffness. Eur Heart J 1992;13:1040-5.
8. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-310.
9. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. Eur Heart J 1990;11:990-996.
10. Nemes A, Forster T, Thury A, Kovacs Z, Boda K, Csanady M. The comparative value of the aortic atherosclerosis and the coronary flow velocity reserve evaluated by stress transesophageal echocardiography in the prediction of patients with aortic stenosis with coronary artery disease. Int J Cardiovasc Imaging 2003;19:371-376.

11. Rajappan K, Rimoldi OE, Camici PG, Bellenger NG, Pennell DJ, Sheridan DJ. Functional changes in coronary microcirculation after valve replacement in patients with aortic stenosis. Circulation 2003;107:3170-3175.
12. Et-Taouil K, Safar M, Plante GE. Mechanisms and consequences of large artery rigidity. Can J Physiol Pharmacol 2003;81:205-211.
13. Schmidtke C, Bechtel J, Hueppe M, Noetzold A, Sievers HH. Size and distensibility of the aortic root and aortic valve function after different techniques of the ross procedure. J Thorac Cardiovasc Surg 2000;119:990-997.
14. Rajappan K, Melina G, Bellenger NG, Amrani M, Khaghani A, Pennell DJ, et al. Evaluation of left ventricular function and mass after Medtronic Freestyle versus homograft aortic root replacement using cardiovascular magnetic resonance. J Heart Valve Dis 2002;11:60-65; discussion 66.

CHAPTER 12

Real-Time Three-Dimensional Echocardiography for Evaluation of Regional Aortic Stiffness

European Journal of Echocardiography 2007; 8: 161-162

Attila Nemes

Marcel L. Geleijnse

Osama I.I. Soliman

Ashraf M. Anwar

Wim B. Vletter

Folkert J. ten Cate

Abstract

Aortic stiffness is an important predictor of cardiovascular morbidity and mortality. Non-invasive measurement of aortic stiffness is a promising challenge for echocardiography. The most important limitation of previous studies was that regional differences for aortic stiffness were not taken into consideration. In our patient, we demonstrated the usefulness of real-time three-dimensional echocardiography in assessment of regional aortic stiffness.

Introduction

Stiffness of large arteries is an important predictor of cardiovascular morbidity and mortality (1). Two-dimensional transthoracic (TTE) and transoesophageal echocardiography (TEE) are both useful methods for the evaluation of stiffness in different aortic regions calculated from aortic and blood pressure data (2-5). Drozdz *et al.* demonstrated that three-dimensional TEE has a strong potential for regional aortic stiffness measurements using horizontal cross-sectional imaging of the vessel (6). The objective of the present methodological study was to demonstrate the usefulness of real-time three-dimensional transthoracic echocardiography (RT3DE) for regional assessment of aortic stiffness. For this aim we demonstrate a case in which the aortic arch was evaluated with RT3DE. To our knowledge this has not been described before.

Methods

RT3DE was performed with a Philips Sonos 7500 ultrasound system (Philips, Best, The Netherlands) attached to an X4 matrix array tranducer equipped with a 3D data acquisition software package. The 3D data sets acquired from the supraclavicular window were analysed off-line with assistance of the TomTec 4D Echo-View 5.3 workstation (TomTec Inc.,

Unterschleissheim, Germany). The aortic lumen can be divided into several segments allowing regional measurements of aortic stiffness. Several indices are used to describe and quantify the physical behaviour of vessels in response to an intraluminal force. For the evaluation of *aortic stiffness index β*, the following formula is used: ln(PS/PD)/(ΔD/DD), where PS and PD are the systolic and diastolic blood pressures, DD is the aortic diastolic diameter, ΔD is the systolic minus diastolic aortic diameter and 'ln' is the natural logarythm. For this elasticity parameter, ΔD, DD, PS and PD measurements are necessary.

According to this methodology, we evaluated aortic stiffness with RT3DE in a 24 year-old healthy man. From the supraclavicular window, the aortic arch, the distal part of the ascending aorta and the proximal part of the descending aorta were visualized. As seen in Figure 1, the cut planes from the 3D data sets that visualized the aorta "en-face" could be easily reconstructed. The reconstructed images allowed the segmental evaluation of aortic cross-sections at different levels. Regional β values were calculated using the blood pressure data (122/80 mm Hg) and regional aortic systolic and diastolic diameters.

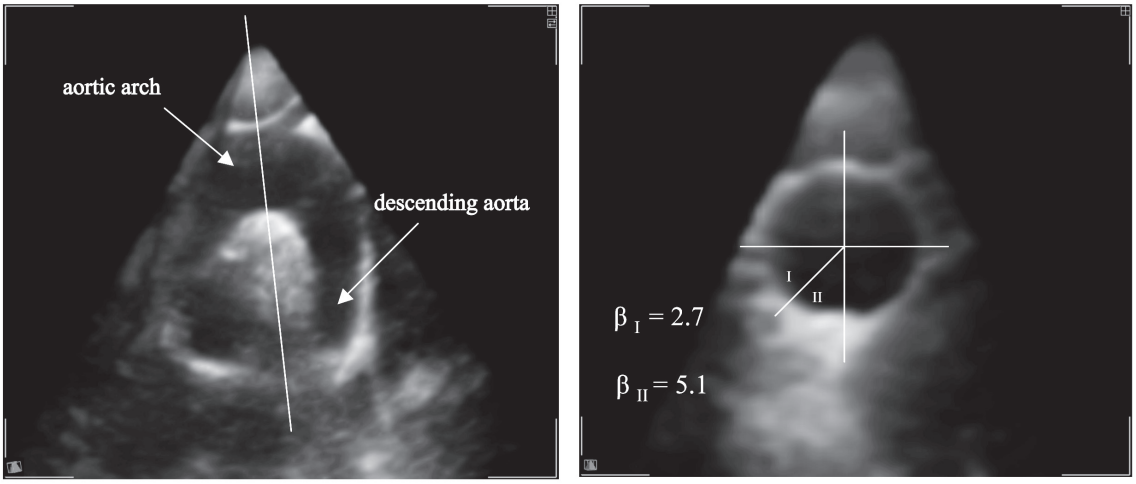


Figure 1 a/b. Regional evaluation of aortic arch stiffness. By division of the aortic arch by coaxial planes into 2 segments with RT3DE. Regional aortic stiffness indices (β) could be calculated in each segment.

Discussion

Aortic stiffness is an important predictor of cardiovascular morbidity and mortality (1). Non-invasive measurement of aortic stiffness is a promising challenge for echocardiography. In previous studies, it has been demonstrated that aortic stiffness can be measured during TTE and TEE examinations (2-5). The most important limitation of these studies was that regional differences for aortic stiffness were not taken into consideration. Regional stiffness of the descending aorta can be characterized by 3D-TEE using horizontal aortic cross-sectional images (6). In our patient, we demonstrated the usefulness of RT3DE in assessment of regional aortic stiffness. However, it should be noted that the echocardiographic window quality (which is somewhat lower compared to two-dimensional TTE) is still a limitation for 3D imaging in some patients. Theoretically, as evidenced in ventricular quantification and carotid artery studies, use of an echo contrast agent may improve aortic image quality (7,8).

References

1. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236-1341.
2. Nemes A, Forster T, Csanady M, Gruber N. Indices of aortic distensibility and coronary flow velocity reserve in patients with different grades of aortic atherosclerosis. Int J Cardiovasc Imaging 2004;20:271-277.
3. Nemes A, Forster T, Csanady M. Decreased aortic distensibility and coronary flow velocity reserve in patients with significant aortic valve stenosis with normal epicardial coronary arteries. J Heart Valve Dis 2004;13:567-573.
4. Nemes A, Forster T, Gruber N, Csanady M. Coronary flow velocity reserve and indices describing aortic distensibility in patients after coronary angiography. Int J Cardiol 2004;96:29-33.
5. Eren M, Gorgulu S, Uslu N, Celik S, Dagdeviren B, Tezel T. Relation between aortic stiffness and left ventricular diastolic function in patients with hypertension, diabetes, or both. Heart 2004;90:37-43.
6. Drozdz J, Krzeminska-Pakuola M, Lipiec P, et al. Regional aortic function is correlated with intima-media thickness-insights from three-dimensional echocardiography. J Am Soc Echocardiogr 2005;18:789-794.
7. Ward RP, Mor-Avi V, Lang RM. Assessment of left ventricular function with contrast echocardiography. Cardiol Clin 2004;22:211-219.

8. Ohm C, Bendick PJ, Monash J, et al. Diagnosis of total internal carotid occlusions with duplex ultrasound and ultrasound contrast. Vasc Endovascular Surg 2005;39:237-243.

Summary and conclusions

Summary and conclusions

The aim of this thesis was to study the advances in the evaluation of cardiovascular function by 2D and real-time 3D stress echocardiography and vascular stiffness measurements.

Stress echocardiography is a widely used non-invasive stress modality for the detection of coronary artery disease The *Part A* of the thesis is focusing on this method demonstrating the current status of 2D and real-time 3D echocardiography (RT3DE).

Chapter 2. Our review describes factors affecting sensitivity and specificity during dobutamine stress echocardiography. This analysis suggests that the reported sensitivity of dobutamine stress echocardiography is higher and the specificity lower than expected in clinical practice. The reason can be the inappropriate inclusion of patients with prior myocardial infarction, definition of positive DSE and the presence of referral bias.

From pooled data, **Chapter 3** demonstrates that dobutamine stress echocardiography carries a definite, albeit small, risk. Life-threatening complications occurred in approximately one out of 400 patients. Before a stress stress is ordered, this risk should always be carefully weighted against the expected diagnostic or prognostic benefit.

The use of ultrasound contrast can have a role in the improvement of image quality. Because of safety concerns we systematically reviewed a consecutive series of patients all adverse effects of SonoVue® in our echocardiographic laboratory. The reported incidence of adverse effects of SonoVue® echo contrast in our small initial serie of cardiac patients seems higher than those reported in a company post-marketing analysis and await confirmation (**Chapter 4**).

Chapter 5 provides an overview of the current status of stress RT3DE emphasizing its advantages over stress 2D echocardiography but showing its current technical limitations. RT3DE is easy to learn and a less time consuming imaging modality, which sees the left ventricle (LV) as it truly is. With stress RT3DE, at each stress level only one 3D data acquisition from one window is needed, which makes a 3D examination faster than conventional 2D stress imaging. Another advantage can be, that from the acquired 3D volumetric data sets, matching views at baseline and at different levels of stress can be reconstructed for a precise comparison of identical segments. RT3DE even allows the anyplane evaluation of LV helping to create short-axis views at different LV levels that may be easier to understand by other (non-cardiologists) physicians. RT3DE thus offers several advantages over 2D echocardiography in the evaluation of LV function. Future studies in real-clinical practice will show the clinical value of RT3DE over 2D echocardiography. In our opinion this imaging modality is currently still hampered by some major technical limitations. Multibeat frame composition, limited spatial resolution and large footprint of the special matrix-array transducer actually form the major technical limitations. However, most of these limitations may be overcome in the near future. With the development of more advanced automated border detection software, we can expect a decrease in inter-observer variability associated with visual scoring of segmental wall motion. Reduction of transducer footprint size will further reduce rib shadowing. If 3D image quality can be brought to a comparable level as 2D image quality, stress RT3DE may be more suitable for such automated analysis than stress 2D echo because 3D images offer higher information content with complete LV visualization. Provided that all these technical improvements will occur stress RT3DE may become an important diagnostic test of the future.

Using recently available RT3DE equipment, our results demonstrate that a relatively high number of myocardial segments are not adequately visualized with conventional stress

RT3DE (146 of the 612 segments, 24%), but contrast-enhancement significantly decreases the number of non-available myocardial segments (59 of the 612 segments, 10%) and improves interobserver agreement for diagnosis of myocardial ischemia (study agreement from 72% to 89%) (**Chapter 6**).

Moreover, it has been demonstrated that addition of parasternal to apical acquisition of contrast RT3DE data decreases the number of non-visualised segments (from 9% to 4%) and improves mean image quality (from 2.43 to 2.74, $p < 0.05$) (**Chapter 7**).

Finally, our case report demonstrates that cropped long- and short-axis images of LV during contrast-enhanced stress RT3DE are comparable to magnetic resonance images, which is a so-called `gold standard` for LV function imaging (**Chapter 8**).

Part B of the thesis is focusing on the evaluation of aortic stiffness in special patients populations.

Aortic stiffness has been shown as a major contributory factor to cardiovascular morbidity and mortality. M-mode echocardiography in combination with non-invasive blood pressure measurements offers an opportunity to characterize vascular stiffness by calculating different stiffness indices. Interestingly, despite the widely available literature with this method there is little experience with storage diseases as glycogenosis type II (Pompe's disease) (**Chapter 9**) and mucopolysaccharidosis type I (**Chapter 10)**. These disorders are associated with enzyme deficiencies resulting in accumulation of deposits in different tissues. Our studies suggested that aortic stiffness is increased in these storage diseases before morphological alterations can be found. However, further follow-up studies are needed to examine arterial elasticity using more reliable methods (RT3DE, magnetic resonance imaging or invasive measurements etc.). Future enzymatic therapies may be followed on the effect of vascular distensibility by the

methods described in the present thesis. Moreover, studies of stiffened aorta on coronary perfusion in these patient populations are also warranted.

In recent studies increased aortic stiffness has been demonstrated in valvular aortic stenosis (AS) as an early manifestation of the atherosclerotic process (endothelial dysfunction), decreased perfusion of the aorta or other factors beyond physical pressure effects. However, the long-term effect of aortic valve replacement on aortic elasticity has never been assessed. The present study found a continuous improvement in aortic distensibility during a 1-year follow-up after surgery. One of the possible explanations for improvement in vascular elasticity may be recovery of damaged aortic root endothelium, which has an important role in the production of vasorelaxant factors and pressure changes in the proximal aorta. However, further long-term follow-up studies are required using other methods confirming our findings mainly evaluating the different kinds of valve types and their effect on flow profile and aortic distensibility (**Chapter 11**).

One of the main limitations of these studies is that regional differences in aortic stiffness at segments of the aortic wall are not taken into consideration. Our report demonstrates that RT3DE offers a special aspect on evaluation of regional aortic stiffness. Further studies are warranted in large patient population in comparison with invasive direct measurements for the evaluation of regional aortic stiffness (**Chapter 12**).

Conclusions. Recent advances in ultrasound technology have shown its advantages in clinical cardiology such as real-time 3D echocardiography and vascular stiffness assessment. Despite current technological limitations as has been described, these new technologies have provided insight into understanding of cardiac and vascular pathophysiology. Limitations of RT3DE are transducer footprint size, frame rate at higher heart rates and image quality. Future

improvements in transducer technology such as harmonic 3D imaging, smaller transducers and the use of different transducer materials are already tested for their usefulness in clinical practice. Also newer algorhytms for automatic border detection will decrease current subjectivity of analysis. For evaluation of aortic stiffness more reliable methods like real-time 3D echocardiography or MRI are under development allowing the exact evaluation not only vascular diameter but shape changes during a heart cycle.

Samenvatting en conclusies

Samenvatting en conclusies

Het doel van dit proefschrift is om nieuwe ontwikkelingen te laten zien in de evaluatie van de cardiovasculaire functie en bepalingen van de stijfheid van de grote vaten gebruikmakend van 2D en 3D echocardiografie.

Stress-echocardiografie en met name Dobutamine Stress-Echo (DSE) is een veel voorkomende algemeen gebruikte niet invasieve belastingtest voor de diagnostiek van coronaire hartziekte. Het gedeelte A richt zich op de methodiek van 2D en real-time 3D echo in zijn huidige vorm.

Hoofdstuk 2. Dit overzichtsstuk beschrijft de factoren die sensitiviteit en specificiteit beïnvloeden tijdens DSE. Onze analyse toont aan dat sensitiviteit van DSE hoger en de specificiteit lager is dan verwacht. Een van de redenen is een waarschijnlijk onjuiste inclusie van patiënten met een oud infarct, definitie van DSE en effect van klinische verwijzingen.

In **hoofdstuk 3** tonen we aan dat DSE toch een risico, hoewel klein, geeft op levensbedreigende complicaties. Dit wordt geschat op 1:400 onderzoeken. Dus late te verwachten complicaties moeten afgewogen worden tegen de te verwachten diagnostische informatie.

Het gebruik van ultrasound contrastmiddelen speelt ook een belangrijke rol voor de verbetering van de beeldkwaliteit. Omdat er problemen met veiligheid van deze methode zijn beschreven, hebben wij systematisch een aantal patiënten bestudeerd en gekeken naar de ongewenste effecten van SonoVue®. De incidentie van bijwerkingen in deze kleine serie van patiënten met hartafwijkingen zijn hoger dan die gerapporteerd in een analyse nadat het middel geregistreerd is en uitgevoerd door het bedrijf dat dit middel produceert (**hoofdstuk 4**).

Hoofdstuk 5 geeft een overzicht van de huidige status van stress real-time 3D echo en benadrukt de voordelen boven stress 2D echo, maar toont ook de huidige technische limitaties van de techniek. Real-time 3D echo is makkelijk te leren en minder tijdrovend dan de huidige technieken. Met behulp van stress real-time 3D is op elk niveau van de stress alleen een 3D data set nodig van één echo window. Dit maakt een 3D onderzoek sneller dan het conventionele 3D stress onderzoek. Een ander voordeel is dat van de opgenomen 3D volumetrische datasets exact dezelfde doorsneden, zowel in rust als van de verschillende niveaus van stress kunnen worden gereconstrueerd. Dat maakt een precieze vergelijking van identieke segmenten mogelijk. Real-time 3D kan ook andere doorsneden construeren van bijvoorbeeld de korte as op verschillende niveaus van de linker kamer. Real-time 3D geeft dus verschillende voordelen boven 2D echo in de evaluatie van de linker kamerfunctie. Toekomstige studies met deze techniek in de echte klinische praktijk zullen de klinische waarde van de real-time 3D boven 2D echo laten zien. Wij zijn van mening dat deze beeldvormende techniek toch nog behoorlijke technische beperkingen kent. Er is een veelheid van opnamebeelden nodig om een beeld te construeren. Er is beperkte resolutie ten gevolge van de grootte van de transducer. De meeste van deze beperkingen zullen in de toekomst worden overwonnen. Met de ontwikkeling van geavanceerde automatische detectie van endocardiale grensvlakken kunnen wij een verlaging verwachten van de interobserver variabiliteit. Een kleinere transducer zal verdere schaduwbeelden verminderen. Als de 3D beeldkwaliteit vergelijkbaar wordt met de huidige 2D beeldkwaliteit zal stress real-time 3D meer bruikbaar zijn voor automatische analyse dan 2D omdat stress 3D een meer compleet beeld van de linker kamer geeft. Als al deze technische beperkingen worden opgelost zal stress real-time 3D echo een belangrijke diagnostische test in de toekomst worden.

Gebruikmakend van nieuwe real-time 3D technologie toont dat een hoog aantal myocardiale segmenten niet kunnen worden zichtbaar gemaakt met conventionele real-time 3D

echo (146 van 612 segmenten, 24%). Echter, het gebruik van ultrasound contrast toont een forse afname van de niet zichtbare segmenten (59 van 612 segmenten, 10%). Het verbetert dus de interobserver variabiliteit. Voor diagnose van myocard ischemie stijgt de overeenstemming tussen 2 observers van 72% naar 89% (**hoofdstuk 6**).

Indien aan de apicale acquisitie ook de parasternale acquisitie wordt toegevoegd met behulp van contrast real-time 3D echo, daalt het aantal niet zichtbare segmenten duidelijk van 9% tot 4% en neemt de beeldkwaliteit toe (van 2.43 tot 2.74 $p < 0.05$) (**hoofdstuk 7**).

Tenslotte, dit laatste klinische voorbeeld laat zien dat lange as en korte as beelden van de linker kamer gedurende stress real-time 3D met behulp van contrastmiddelen een vergelijkbare kwaliteit hebben als dezelfde beelden gemaakt bij de patiënt indien gebruik gemaakt wordt van MRI, wat de gouden standaard voor deze linker kamer beeldvormende techniek is (**hoofdstuk 8**).

Het gedeelte B van dit proefschrift richt zich op de evaluatie van de stijfheid van de aorta in speciale patienten groepen.

Stijfheid van de aorta is een belangrijke factor die bijdraagt aan cardiovasculaire functie kwaliteit en morbiditeit. M-mode echo in combinatie met niet invasieve bloeddrukmeting vormt een mogelijkheid om de vasculaire stijfheid te bepalen. Hoewel deze techniek vrij veel wordt gebruikt is in de literatuur weinig te vinden over de toepassing bij stapelingsziekten zoals ziekte van Pompe (**hoofdstuk 9**) en mucopolysaccharidosis (**hoofdstuk 10**). Deze ziektes zijn geassocieerd met enzymafwijkingen resulterend in accumulatie van neerslagen in de verschillende weefsels. Onze studie laat zien dat de aortastijfheid toegenomen is bij deze stapelingsziekte voordat er morfologische veranderingen worden gevonden. Echter, verdere follow-up studies zijn nodig om onze bevindingen te bevestigen, eventueel gebruikmakend van

realtime 3D en MRI. In de toekomst zullen mogelijk enzymatische therapieën beschikbaar worden waarbij deze methode gebruikt kan worden voor de follow-up van deze patiënten. Verder zijn deze studies nodig naar de stijfheid van de aorta op het effect van de coronaire perfusie in deze patiënten.

In recente publicaties is ook toename van de aortastijfheid beschreven bij valvulaire aortastenose als een vroege manifestatie van aortasclerose, verminderde perfusie van de aorta of andere factoren buiten de bekende factoren die reeds bekend zijn. Echter, de lange termijn effecten van aortaklep vervanging op aorta stijfheid en elasticiteit zijn nooit beschreven. De huidige studie toont een verbetering in de aorta elasticiteit aan gedurende een follow-up van 1 jaar na chirurgie. Een van de verklaringen zou kunnen zijn dat de beschadigde aorta wortel weer wordt hersteld zodat een verbeterd aorta wortel endotheel vaso relaxatie factoren kunnen produceren. Echter, lange termijn studies in deze patiënten is nodig om onze resultaten te bevestigen (**hoofdstuk 11**).

Een van de voornaamste beperkingen van deze studies is dat regionale veranderingen in de aortastijfheid niet in overweging worden genomen. Onze studie laat zien dat realtime 3D een speciaal effect van de evaluatie van de regionale aorta stijfheid laat zien. Verdere studies in grotere patiënten populaties met invasieve directe metingen zijn nodig om deze regionale stijfheid te bepalen (**hoofdstuk 12**).

Conclusies. Huidige verbeteringen in de ultrasound technologie hebben laten zien dat diagnostische verbeteringen in de klinische cardiologie zoals real-time 3D echo en stijfheidbepaling van de vaten kunnen plaatsvinden. Hoewel er nog technologische beperkingen zijn, geven deze nieuwe technologieën toch inzage in de pathofysiologie van hart en bloedvaten. Beperkingen van real-time 3D zijn de grootte van de transducer, het aantal

beelden per seconde dat voornamelijk een beperking is bij hogere hartslagen en beeldkwaliteit. Toekomstige verbeteringen in transducer technologie, zoals harmonische 3D beeldvorming, kleinere transducers en andere transducer materialen zijn al in het stadium van technische evaluatie. Ook nieuwe algoritmes voor betere automatische detectie van endocardiale vlakken zullen nodig zijn. Voor evaluatie van de stijfheid van de aorta zullen meer betrouwbare methodes zoals 3D of MRI ontwikkeld moeten worden om niet alleen de vasculaire diameter maar ook de vorm van de vaten gedurende de hartcyclus te bepalen.

Acknowledgements

Acknowledgements

My stay at the Thoraxcenter and the preparation of this thesis have been important experiences in my professional life. It has been an exciting journey in the field of research and a rich experience in my personal development with regard to my career and being abroad.

First of all, I would like to thank Prof. Dr. Maarten L. Simoons, as my promotor. I thank him for allowing me to be a guest in the Thoraxcenter and for his special final touch in the correction of the thesis.

Second, but not less important, I would like to show my appreciation to Dr. Folkert J. ten Cate, the present head of the Echocardiography Laboratory as my co-promotor. His interest in 3D echocardiography and ideas stimulated my research. I could find him not only the scientist but also a man with broad culture.

I am particularly indebted to Dr. Marcel L. Geleijnse. I am very greatful for the hundreds of hours he has spent in reviewing the articles of this thesis. It is true to say that this project would not have succeeded without his support.

I would like to convey my appreciation to Mrs. Jackie McGhie and Mr. Wim B. Vletter, experts in echocardiography, who provided me with valuable suggestions. I also thank for their co-operation all the technicians of Echocardiography Laboratory and secretaries. I won't forget Rene Frowijn, the 'magician of computers', from whom I always got help with computer problems.

I also would like to highlight the “engineers of the 23th floor”, who helped me to understand the new real-time three-dimensional ultrasound systems. I would like to mention particularly ‘Hans’ J.G. Bosch, who sometimes could very easily explain me complex aspects of ultrasound physics.

I would like to thank Prof. Dr. Tamás Forster, present head of 2nd Department of Medicine and Cardiology Center at the University of Szeged, who allowed and supported me to come here. Thanks to Prof. Dr. Miklós Csanády, previous head of my department, who allowed me to start my clinical and scientific carrier in Szeged.

During my Fellowship I had the opportunity to meet a lot of collegues. It has been for me a unique experience to know them: A.M. Anwar (Egypt), O.I.I. Soliman (Egypt), S.C. Yap (the Netherlands), A.E. van den Bosch (the Netherlands), B.J. Krenning (the Netherlands), K. Caliskan (the Netherlands, Turkey), M. Michels (the Netherlands), R.J. van Geuns (the Netherlands), D.A.M.J. Theuns (the Netherlands), R.F.M. de Coo (the Netherlands), T.W. Galema (the Netherlands), J.H.P. Wilson (the Netherlands), R.G.M. Timmermans (the Netherlands), N.A.M.E. van der Beek (the Netherlands), W.K. Lagrand (the Netherlands).

I would like to thank my parents, who supported me to start my medical carrier. Finally, but not last, I would like to thank my family, especially my wife Viktória and daughter Dorka, who always supported me in my decisions, who listened and comforted me when things were not going well.

Curriculum Vitae

Curriculum Vitae - Dr. Attila Nemes

Date of birth	:	19. December 1972.
Place of birth	:	Szeged, Hungary
Wife	:	Dr. Viktória Nemesné Tóth
Child	:	Dorka Nemes
Working place	:	2nd Department of Medicine and Cardiology Center, Faculty of Medicine, University of Szeged
Address	:	H-6720, Korányi fasor 6, Szeged, Hungary
e-mail	:	nemes@in2nd.szote.u-szeged.hu

Knowledge of language (exams): English (1991), Russian (1990)

Pre-doctoral education:

1991 – 1997 : Albert Szent-Györgyi Medical University, Szeged, Hungary

Post graduate training:

1997 – 2001	:	PhD student
2001 – 2003	:	Resident in Internal Medicine
2003 – 2005	:	Clinical physician

Scientific degrees:

PhD degree (2003, University of Szeged, Hungary)
Thesis: Factors affecting coronary flow velocity reserve and its relations to aortic atherosclerosis
F.E.S.C. (2004) `Fellow of the European Society of Cardiology`

Professional positions:

2005 – present	:	Specialist in Internal Medicine
2005 – 2007	:	Research Scientist (Thoraxcentre, Erasmus MC, Rotterdam, The Netherlands)

Academic duties:

1. Per review for :
   Atherosclerosis, Thrombosis and Vascular Biology
   Canadian Journal of Cardiology
   Diabetes Care
   International Journal of Cardiology
   Journal of American Society of Echocardiography
   Journal of Biomechanics
   Medical Science Monitor

2. Invited grant reviewer : National Medical Research Council of the Ministry of Health of Singapure

3. Invited speaker : World Congress of Cardiology 2006 (2-6 September, 2006, Barcelona, Spain): The influence of aortic compliance on coronary hemodynamics

4. Visits (conferences) : European Society of Cardiology (2000 – 2006)

		American Heart Association (2000, 2002) American College of Cardiology (2002, 2003) Euroecho (1998 - 2006) Alpe-Adria Cardiology Meeting (2001 - 2004) Hungarian Society of Cardiology (1999-2005)
5. Teaching activities	:	Medical students (both hungarian and english): internal medicine, cardiology and echocardiography
6. Scientific prizes	:	Certificate for the lecture presented in the 7th István Cserháti Memorial Meeting, Section Cardiology Prize (20. October 2001, Szeged, Hungary) Special Prize of Youth Presenters for the presentation in 33rd Congress of the South Hungarian Decentrum of the Hungarian Society of Internists, (18-19. April 2002, Szolnok, Hungary) Certificate for the lecture presented in the 8th István Cserháti Memorial Meeting, Section Cardiology Prize (10. October 2003, Szeged, Hungary) Ferenc Adorján prize donated by the Hungarian Institute of Cardiology (2004) Youth Section Prize of the Congress of Hungarian Society of Cardiology (May 2004) Ferenc Markusovszky Prize donated by the Hungarian Medical Journal (May 2005)
7. Scientific results	:	Scientific presentations at conferences: 206 Abstracts in journal: 131 Articles in journal: 70 Sum of impact factors (articles): 86.222
8. Co-promotor	:	Dr. Éva Csajbók. Proposed PhD thesis: Vascular functional alterations in endocrinological disorders (University of Szeged, Hungary)

List of publications

List of publications

1. Nemes A, Forster T, Varga A, Gruber N, Gaál T, Csanády M. Az ischaemiás szívbetegség és a transoesophagealis echocardiographiával az aortában detektált atheroscleroticus plaque-ok súlyosságának kapcsolata [Relationship between ischaemic heart disease and the severity of atherosclerotic aortic plaque detected by transoesophageal echocardiography] Cardiologia Hungarica 1999; 3**:** 117-121

2. Nemes A, Forster T, Pálinkás A, Vass A, Borthaiser A, Ungi I, Thury A, Litvai E, Nádaskay M, Csanády M. A dipyridamol terheléses transoesophagealis echocardiographia segítségével számított coronaria áramlási rezerv klinikai értéke ischaemiás szívbetegségben [The value of coronary flow reserve in ischaemic heart disease measured by dipyridamole stress transoesophageal echocardiography] Orv Hetil 2000; 141**:** 2327-2331

3. Pálinkás A, Marosi Gy, Hornyák E, Forster T, Nemes A, Varga A, Csanády M. Fenyegető paradox embólia esete [Impending paradoxical embolism] Orv Hetil 2000; 141**:** 1517-1521

4. Nemes A, Forster T, Litvai E, Nádaskay M, Vass A, Borthaiser A, Pálinkás A, Gruber N, Csanády M. A coronaria áramlási rezerv és az aorta tágulékonyságát jellemző indexek kapcsolata a coronarographia eredményének ismeretében [Relationship between coronary flow reserve and aortic distensibility indices in patients after coronary angiography] Cardiologia Hungarica 2001; 4**:** 285-289

5. Nemes A, Forster T, Sepp R, Pálinkás A, Thury A, Ungi I, Hőgye M, Csanády M. A transoesophagealis echocardiographiával vizsgált coronaria áramlás jellegzetességei hypertrophiás cardiomyopathia eseteiben [Coronary flow characteristics evaluated by transoeosphageal echocardiography in patients with hypertrophic cardiomyopathy] Cardiologia Hungarica 2002; 4: 203-209

6. Nemes A, Forster T, Pálinkás A, Hőgye M, Csanády M. Coronary flow reserve measured by stress transesophageal echocardiography in hypertrophic cardiomyopathy patients with subvalvular gradient. Kardiol Pol 2002; 57: 96-100

7. Nemes A, Forster T, Varga A, Vass A, Borthaiser A, Pálinkás A, Csanády M. How can the coronary flow reserve be altered by severe aortic stenosis? Echocardiography 2002; 19: 655-659

8. Nemes A, Forster T, Kovács Z, Thury A, Ungi I, Csanády M. The effect of aortic valve replacement on coronary flow reserve in patients with a normal coronary angiogram. Herz 2002; 27: 780-784

9. Pálinkás A, Varga A, Nyúzó B, Gruber N, Forster T, Nemes A, Horváth T, Fogas J, Boda K, Sepp R, Hőgye M, Vass A, Csanády M. A bal pitvari fülcse áramlás szerepe a cardioversio rövid és hosszú távú sikerességének előrejelzésében nem valvularis eredetű pitvarfibrilláció fennállásakor [Clinical role of flow velocity of left atrial auricle for prediction of short and long-term success of cardioversion in patients with non-valvular atrial fibrillation] Orv Hetil 2002; 143: 2035-2041

10. Nemes A, Forster T, Kovács Zs, Kósa I, Feke Gy, Szepesvári Sz, Kócsy J, Csanády M. Alkalmas-e a terheléses transoesophagealis echocardiographiával vizsgált coronaria áramlási rezerv az aorta stenosisos és a coronaria betegek elkülönítésére? [Is coronary flow reserve evaluated by stress transoesophageal echocardiography a suitable method for the differentiation between patients with aortic valve stenosis and coronary artery disease?] Cardiologia Hungarica 2003; 33: 105-109

11. Nemes A, Forster T, Thury A, Kovács Zs, Boda K, Csanády M. The comparative velue of the aortic atherosclerosis and the coronary flow velocity reserve evaluated by stress transesophageal echocardiography in the prediction of patients with aortic atherosclerosis

with coronary artery disease. Int J Cardiovasc Imag 2003; 19: 371-376

12. Pálinkás A, Varga A, Nagy V, Nyúzó B, Eller J, Boda K, Nemes A, Gruber N, Halmai L, Károlyi H, Papp I, Kovács Zs, Forster T, Csanády M. A bal pitvari fülcse áramlás kapcsolata klinikai és echocardiographiás paraméterekkel pitvarfibrilláló betegeknél [Relation of left atrial appendage flow to clinical and echocardiographic parameters in patients with atrial fibrillation] Cardiologia Hungarica 2003; 33: 15-22

13. Nemes A, Forster T, Neu K, Kovács Zs, Csanády M. A coronaria áramlási rezerv összefüggése a balkamra hypertrophiával hypertoniás betegekben [Relationship between coronary flow reserve and hypertensive left ventricular hypertrophy] Magy Belorv Arch 2004; 57: 174-178

14. Nemes A, Forster T, Gruber N, Csanády M. A transoesophagealis echocardiographia segítségével számított, az aorta descendens tágulékonyságát jellemző indexek értéke koszorúér-betegségben és aortastenosis esetén [Aortic distensibility indices evaluated by transoesophageal echocardiography in patients with coronary artery disease or aortic valve stenosis] Orv Hetil 2004; 145: 1931-1935

15. Nemes A, Forster T, Csanády M. Coronary flow reserve in patients with aortic valve stenosis – the review of the literature and own observations. Pol Przeglad Kardiol 2004; 6: 203-207

16. Nemes A, Forster T, Gruber N, Csanády M. Coronary flow velocity reserve and indices describing aortic distensibility in patients after coronary angiography. Int J Cardiol 2004; 96: 29-33

17. Nemes A, Forster T, Csanády M, Gruber N. Coronary flow velocity reserve and the indices of aortic distensibility in patients with different grades of aortic atherosclerosis. Int J Cardiovasc Imag 2004; 20: 271-277

18. Nemes A, Forster T, Csanády M. Decreased aortic distensibility and coronary flow velocity

reserve in patients with significant aortic valve stenosis with normal epicardial coronary arteries. J Heart Valve Dis 2004; 13: 567-573

19. Nemes A, Neu K, Forster T, Gruber N, Csanády M. Relationship between hypercholesterolemia, lipid-lowering therapy and coronary flow velocity reserve evaluated by stress transesophageal echocardiography in patients with a negative coronary angiogram. Echocardiography 2004; 27: 37-41

20. Nemes A, Forster T, Ungi I, Nagy V, Neu K, Kutyifa V, Varga A, Vass A, Pálinkás A, Csanády M. A terheléses transoesophagealis echocardiographia során számított koronáriaáramlási rezerv szerepe a bal koronária leszálló ági intervenciók sikerességének megítélésében - egy ötéves követéses vizsgálat eredményei [Coronary flow reserve evaluated by stress transoesophageal echocardiography in the evaluation of success on the left anterior descending coronary artery interventions – Results of a 5-year follow-up] Cardiologia Hungarica 2005; 35: 52-58

21. Nemes A, Forster T, Csanády M. Aortic distensibility in coronary artery disease and in aortic stenosis. Acta Cardiol 2005; 60: 55-56

22. Nemes A, Vletter WB, Scholten MF, ten Cate FJ. Contrast echocardiography for perfusion in right ventricular cardiomyopathy. Eur J Echocardiogr 2005; 6: 470-472

23. Nemes A, Lengyel C, Forster T, Várkonyi TT, Takács R, Nagy I, Kempler P, Lonovics J, Csanády M. Coronary flow reserve, insulin resistance and blood pressure response to standing in patients with normoglycaemia: ithere a relationship? Diabetic Med 2005; 22: 1614-1618

24. Nemes A, Neu K, Forster T, Kovács Zs, Csanády M. Coronary flow velocity reserve is diminished in hypertensive left ventricular hypertrophy. Kardiol Pol 2005; 62: 1-5

25. Nemes A, Forster T, Ungi I, Nagy V, Vass A, Pálinkás A, Varga A, Csanády M. The

coronary flow velocity reserve measured by stress transoesophageal echocardiography evaluates the success of coronary interventions - Results of a 5-year follow-up. Scand Cardiovasc J 2005; 39: 286-292

26. Nemes A, Forster T, Csanády M. The evaluation of aortic atherosclerosis and distensibility in aortic valve stenosis – The role of transesophageal echocardiography. J Thorac Cardiovasc Surg 2005; 130: 1483-1484

27. Pálinkás A, Nagy E, Varga A, Farkas A, Nemes A, Sepp R, Forster T. „In situ" thrombusképződés a fossa ovalisban nyitott foramen ovale nélkül: transoesophagealis echocardiographiás bizonyíték bizonyíték [„In situ" thrombus formation in the fossa ovalis without open foramen ovale: confirmation by transoesophageal echocardiography] Cardiologia Hungarica 2005; 35: 227-229

28. Geleijnse ML, Nemes A, Vletter WB. Response to: "Contrast-enhanced real-time 3-dimensional dobutamine stress echocardiography" J Am Soc Echocardiogr 2006; 19: 1076

29. Nemes A, Geleijnse ML, van Geuns RJ, Caliskan K, Michels M, Soliman OI, McGhie JS, ten Cate FJ. Evaluation of pericardial hydatid cysts by different echocardiographic imaging modalities. Int J Cardiovasc Imag 2006; 22: 647-651

30. Nemes A, Forster T, Kovacs Z, Csanady M. Is the coronary flow velocity reserve improvement after aortic valve replacement for aortic stenosis transient? Results of a 3-year follow-up. Heart Vessels 2006; 21: 157-161

31. Nemes A, Geleijnse ML, Soliman OI, ten Cate FJ. Predictive value of combination of coronary flow reserve with aortic distensibility indices. Eur Heart J 2006; 27: 2607-2608

32. Nemes A, Vletter WB, ten Cate FJ. Real-time 3-dimensional echocardiographic evaluation of left ventricular thrombus – a live case. Neth Heart J 2006; 14: 267

33. Nemes A, McGhie JS, ten Cate FJ. Real-time 3-dimensional evaluation of aortic dissection. J

Am Soc Echocardiogr 2006; 19: 108.e1-108e.3

34. Nemes A, Forster T, Csanády M. Relationship between coronary flow reserve and aortic stiffness. Am J Physiol-Heart Circ Physiol 2006; 209: H1311

35. Nemes A, Forster T, Geleijnse ML, ten Cate FJ, Csanady M. The effect of aortic valve replacement of coronary flow reserve. J Thorac Cardiovasc Surg 2006; 132: 726-727

36. Nemes A, Lagrand WK, McGhie JS, ten Cate FJ. Three-dimensional transoesophageal echocardiography in the evaluation of aortic valve destruction by endocarditis. J Am So Echocardiogr 2006; 19: 355.e13-355.e14

37. Nemes A, Gavaller H, Hogye M, Palinkas A, Forster T, Csanady M. Transthoracic echocardiographic evalaution of aortic distensibility in a Takayasu arteritis patient. J Cardiac Surg 2006; 21: 593-595

38. Anwar AM, Geleijnse ML, Soliman OI, McGhie JS, Nemes A, ten Cate FJ. Evaluation of rheumatic tricuspid valve stenosis by real-time three-dimensional echocardiography. Heart 2007; 93: 363-364

39. Geleijnse ML, Krenning BJ, Soliman OI, Nemes A, Galema TW, ten Cate FJ. Dobutamine stress echocardiography for the detection of coronary artery disease in women. Am J Cardiol 2007; 99: 714-717

40. Nemes A, Galema TW, Geleijnse ML, Soliman OI, Yap SC, Anwar AM, ten Cate FJ. Aortic valve replacement for aortic stenosis is associated with improved aortic distensibility at long-term follow-up. Am Heart J 2007; 153: 147-151

41. Nemes A, Thury A, Forster T, Boda K, Csanády M. Grade of aortic atherosclerosis: A valuable adjunct to coronary flow velocity reserve in the evaluation of coronary artery disease. Ups J Med Sci 2007; 112: 73-84

42. Nemes A, Forster T, Csanady M. Impaired coronary flow velocity reserve and aortic distensibility in patients with untreated hypercholesterolemia - an echocardiographic study. Int J Cardiovasc Imag 2007; 23: 15-23

43. Nemes A, Geleijnse ML, Soliman OI, Anwar AM, Vletter WB, ten Cate FJ. Real-time three-dimensional echocardiography for regional evaluation of aortic stiffness. Eur J Echocardiogr 2007; 8: 161-162

44. Nemes A, Geleijnse ML, Krenning BJ, Soliman OI, Anwar AM, Vletter WB, ten Cate FJ. Usefulness of ultrasound contrast agent to improve image quality during real-time three-dimensional stress echocardiography. Am J Cardiol 2007; 99: 275-278

45. Nemes A, Forster T, Csanady M. Simultaneous evaluation of coronary flow velocity reserve and aortic distensibility indices in hypertension. Heart Vessels 2007; 22: 73-78

46. Soliman OI, Theuns DA, Geleijnse ML, Anwar AM, Nemes A, Caliskan K, Vletter WB, Jordaens LJ, ten Cate FJ. Spectral pulsed-wave tissue Doppler imaging lateral-to-septal delay fails to predict clinical or echocardiographic outcome after cardiac resynchronization therapy. Europace 2007; 9: 113-118

47. Anwar AM, Soliman OI, Geleijnse ML, Michels M, Vletter WB, Nemes A, ten Cate FJ. Assessment of left atrial ejection force in hypertrophic cardiomyopathy using real-time three-dimensional echocardiography. J Am Soc Echocardiogr, *in press*

48. Anwar AM, Soliman OI, Geleijnse ML, Nemes A, Vletter WB, ten Cate FJ. Assessment of left atrial volume and function by real-time three-dimensional echocardiography. Int J Cardiol, *in press*

49. Anwar AM, Soliman OI, Nemes A, Krenning BJ, van Geuns RJ, Geleijnse ML, ten Cate FJ. Assessment of mitral annulus size and function by real-time three-dimensional echocardiography in cardiomyopathy: Comparison with magnetic resonance imaging. J Am

Soc Echocardiogr, *in press*

50. Anwar AM, Geleijnse ML, Soliman OI, McGhie JS, Frowijn R, Nemes A, van den Bosch AE, Galema TW, ten Cate FJ. Assessment of normal tricuspid valve anatomy in adults by real-time three-dimensional echocardiography. Int J Cardiovasc Imag, *in press*
51. Anwar AM, Geleijnse ML, Soliman OI, Nemes A, ten Cate FJ. Left Atrial Frank Starling Law Assessed by Real-time Three-dimensional echocardiographic Left Atrial Volume Changes. Heart, *in press*
52. Anwar AM, Soliman OI, Ten Cate FJ, Nemes A, McGhie JS, Krenning BJ, van Geuns RJ, Galema TW, Geleijnse ML. True mitral annulus diameter is underestimated by two-dimensional echocardiography as evidenced by real-time three-dimensional echocardiography and magnetic resonance imaging. Int J Cardiovasc Imag, *in press*
53. Anwar AM, Soliman OI, Nemes A, van Geuns RJ, Geleijnse ML, Ten Cate FJ. Value of assessment of tricuspid annulus: real-time three-dimensional echocardiography and magnetic resonance imaging. Int J Cardiovasc Imag, *in press*
54. Anwar AM, Soliman OI, Nemes A, Geleijnse ML, Ten Cate FJ. An intergated approach to determine left atrial volume, mass and function in hypertrophic cardiomyopathy by two-dimensional echocardiography. Int J Cardiovasc Imag, *in press*
55. Geleijnse ML, Krenning BJ, Soliman OI, Nemes A, Galema TW, ten Cate FJ. Diagnostic value of dobutamine stress echocardiography in patients with normal wall motion at rest. Echocardiography, *in press*
56. Nemes A, Caliskan K, Geleijnse ML, Soliman OI, Anwar AM, ten Cate FJ. Alterations in aortic elasticity in noncompaction cardiomyopathy. Int J Cardiovasc Imag, *in press*
57. Nemes A, Gavaller H, Csajbok E, Julesz J, Forster T, Csanady M. Aortic stiffness is increased in acromegaly - a transthoracic echocardiographic study. Int J Cardiol, *in press*

58. Nemes A, Soliman OI, Geleijnse ML, Anwar AM, van der Beek NA, van Doorn PA, Gavaller H, Csajbok E, ten Cate FJ. Increased aortic stiffness in glycogenosis type 2 (Pompe's disease). Int J Cardiol, *in press*

59. Nemes A, Forster T, Csanady M. Patients with aortic valve stenosis and Type 2 diabetes have similar coronary flow reserve and aortic distensibility compared with non-diabetic patients with aortic valve stenosis. Diabetes Res Clin Prac, *in press*

60. Nemes A, Forster T, Csanady M. Reduced coronary flow velocity reserve and aortic distensibility in patients with diabetes mellitus with negative coronary angiograms. Can J Cardiol, *in press*

61. Nemes A, Forster T, Geleijnse ML, Kutyifa V, Neu K, Soliman OI, ten Cate FJ, Csanady M. The additional prognostic power of diabetes mellitus on coronary flow reserve in patients with suspected coronary artery disease. Diabetes Res Clin Prac, *in press*

62. Nemes A, Geleijnse ML, Vletter WB, Krenning BJ, Soliman OII, ten Cate FJ. Role of parasternal data acquisition during contrast enhanced real-time three-dimensional echocardiography. Echocardiography, *in press*

63. Rosztoczy A, Vass A, Izbeki F, Nemes A, Rudas L, Csanady M, Lonovics J, Forster T, Wittmann T. The evaluation of gastro-oesophageal reflux and oesophagocardiac reflex in patients with angina-like chest pain following cardiologic investigations. Int J Cardiol, *in press*

64. Soliman OI, Knaapen P, Geleijnse ML, Dijkmans PA, Anwar AM, Nemes A, Michels M, Vletter WB, Lammertsma AA, ten Cate FJ. Assessment of intra- and extra-vascular mechanisms of myocardial perfusion abnormalities in obstructive hypertrophic cardiomyopathy by myocardial contrast echocardiography. Heart, *in press*

65. Soliman OI, Theuns DAMJ, ten Cate FJ, Anwar AM, Nemes A, Vletter WB, Jordaens L,

Geleijnse ML. Baseline predictors of cardiac events after cardiac resynchronization therapy in patients with ischemic and non-ischemic etiology. Am J Cardiol, *in press*

66. Soliman OI, Krenning BJ, Geleijnse ML, Nemes A, van Geuns RJ, Kirschbaum SW, Anwar AM, Galema TW, Vletter WB, ten Cate FJ. Quantification of left ventricular volumes and function in patients with cardiomyopathies by real-time three-dimensional echocardiography. A head-to-head comparison between two different semi-automated endocardial border detection algorithms. J Am Soc Echocardiogr, *in press*
67. Soliman OI, Geleijnse ML, Meijboom FJ, Nemes A, Kamp O, Nihoyannopoulos P, Masani N, Feinstein S, ten Cate FJ. The use of contrast echocardiography for the detection of cardiac shunts. Eur J Echocardiogr, *in press*
68. Soliman OI, Krenning BJ, Geleijnse ML, Nemes A, van Geuns RJ, Baks T, Anwar AM, Galema TW, Vletter WB, ten Cate FJ. A comparison between QLAB and TomTec full volume reconstruction for real-time three-dimensional echocardiographic quantification of left ventricular volumes. Echocardiography, *in press*
69. Soliman OI, Timmermans RGM, Nemes A, Vletter WB, Wilson JHP, ten Cate FJ, Geleijnse ML. Cardiac abnormalities in adults with the attenuated form of mucopolysaccharidosis type I. J Inherit Metab Dis, *in press*
70. Yap SC, van Geuns RJ, Nemes A, Meijboom FJ, McGhie JS, Geleijnse ML, Simoons ML, Roos-Hesselink. Measurement of left ventricular mass by real-time three-dimensional echocardiography is more accurate than convential echocardiography in patients with congenital aortic stenosis. Eur J Echocardiogr, *in press*