

DOBUTAMINE STRESS DOPPLER AND ECHOCARDIOGRAPHY

(Dobutamine stress Doppler en echocardiografie)

Proefschrift

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. Dr. P.W.C. Akkermans M. Lit.
en volgens het besluit van het College van Dekanen.
De openbare verdediging zal plaats vinden
op woensdag 21 September 1994 om 13.45 uur
door

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geboren te Cairo

Promotiecommissie

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Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

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This thesis is dedicated
to the soul of my father, to my mother
and to Maria for her selfless support and devotion.

CHAPTER 1

INTRODUCTION

Myocardial ischaemia results from a supply-demand imbalance between coronary blood flow and myocardial metabolic requirements leading to a cascade of events that alters all functions of the myocardium.¹ The sequence of events during myocardial ischaemia begins with maldistribution of the coronary blood flow between territories supplied by the stenotic and non stenotic coronary arteries. This is followed by left ventricular (LV) diastolic dysfunction and regional wall motion abnormalities.²⁻⁴ The latest events are ischaemic electrocardiographic (ECG) changes and angina.^{2,3} Several studies²⁻⁵ suggested that the impairment of LV diastolic function precedes the development of systolic dysfunction and that changes in diastolic parameters may be considered the earliest indicators of myocardial ischaemia. Because of these observations there is a clinical interest in investigating regional as well as global LV performance and to consider both systolic and diastolic function.

Advanced degrees of coronary arterial obstruction may exist without signs of myocardial ischaemia or underperfusion at rest.⁶ Manifestations of myocardial ischaemia can be provoked by a variety of stimuli. Provocative stress tests can be divided into two groups according to their influence on the pathophysiological mechanism of ischaemia: (a) stress modalities that induce or enhance maldistribution of myocardial blood flow and therefore diminish the coronary flow to an area supplied by a stenotic coronary artery "coronary steal". These include pharmacologic coronary vasodilators such as dipyridamole⁷ and adenosine⁸ or vasopressors such as ergonovine; and (b) stress modalities that primarily increase myocardial oxygen demand by increasing heart rate and contractility. These include physical exercise,⁹⁻¹¹ rapid atrial pacing,¹² mental stress,¹³ cold pressor test,¹⁴ and inotropic agents. These include isoproterenol,¹⁵ dopamine,¹⁶ dobutamine¹⁷ and more recently arbutamine.¹⁸ Among several non-exercise stress modalities dobutamine and dipyridamole are the most commonly used pharmacologic stress agents in conjunction with myocardial perfusion scintigraphy, echocardiography and Doppler in the diagnosis and prognosis of patients with coronary artery disease (CAD).^{17,19,20} There is evidence from experimental²¹ and clinical²² studies that dobutamine is more effective

in precipitating myocardial dysfunction than dipyridamole and is well suited for imaging modalities that rely on functional assessment of CAD.

The presence of CAD is identifiable on the basis of anatomic narrowing of coronary arteries, and the noninvasive detection of stress-induced markers of myocardial ischaemia. These include ECG changes compatible with ischaemia, scintigraphic perfusion defects, regional wall motion abnormalities or global systolic and diastolic abnormalities. Coronary angiography accurately identifies the presence of anatomic narrowing of coronary arteries, but may fail to predict the functional consequences.^{23,24} Exercise ECG has a well established value for the diagnosis and prognosis of patients with CAD. However, the limited sensitivity and specificity and the inability of the exercise ECG to provide accurate assessment of the localization, extent and severity of the jeopardized myocardium have led to its combination with cardiac imaging techniques.²⁵ Myocardial perfusion scintigraphy and radionuclide ventriculography are well established techniques for the identification of perfusion defects, wall motion abnormalities and changes in global LV systolic and diastolic function during different forms of stress.^{26,27} The use of radionuclide techniques requires the use of a radioisotope and the availability of a gamma camera and is relatively expensive for routine use. When factors such as biological hazards, ease of use, applicability during or immediately after stress and costs of installation and maintenance are taken into account, echo-Doppler may be the most cost-effective technique.²⁸ Echocardiographic techniques used with exercise and non-exercise stress protocols have been shown to provide information regarding the presence, severity and distribution of CAD with a comparable sensitivity and specificity to radionuclide techniques.²⁹⁻³¹ Doppler techniques offer alternative and complementary indicators of ischaemic impairment of both systolic and diastolic global LV function and has been validated against other invasive and non-invasive techniques.³²⁻³⁴ Abnormalities of Doppler-derived parameters of either systolic or diastolic LV performance in response to physiologic and pharmacologic interventions have been described in few studies. These studies suggested that Doppler examination might be a useful adjunct to stress testing for the identification of patients with CAD.^{19,20,35,36}

Studies presented in this thesis:

In *Chapter 1* an introduction of the thesis is presented.

In *chapter 2* the general methodology used in this research is described. The pharmacological effects of dobutamine and the rationale of its use as a stress agent; methods of assessment of LV wall motion by echocardiography; and methods of Doppler assessment of LV systolic and diastolic function and the physiologic and pathologic factors that influence Doppler parameters are presented in Chapter 2.

In *chapter 3* the advantages of adding atropine to dobutamine to perform stress echocardiography will be discussed. Beta blockers partially antagonize the chronotropic and inotropic effects of dobutamine. Withdrawal of beta blockers may be impractical in patients with CAD. To retain the inotropic effect of dobutamine, but to overcome the lack of chronotropic effect, we combined atropine with dobutamine and assessed the safety and diagnostic accuracy of this combined pharmacologic stress test for detecting CAD.

In *chapter 4* the initial experience in the use of dobutamine-atropine stress echocardiography for assessment of patients before and early after angioplasty is discussed. The effect of successful angioplasty has previously been assessed by exercise echocardiography,³⁷ dipyridamole echocardiography,³⁹ and perfusion scintigraphy.³⁸ We used dobutamine stress echocardiography to assess the functional effect of the change in myocardial perfusion early after angioplasty.

In *chapters 5 and 6* Doppler-derived parameters of global LV systolic and diastolic function and their response to high dose dobutamine is presented. Doppler parameters of LV ejection and filling have been used to detect ischaemia induced by dipyridamole, exercise or pacing stress tests.^{20,35,36} Doppler reports on improvements in resting LV diastolic function early after angioplasty are conflicting.^{40,41} Studies on LV filling during exercise are impractical with echo-Doppler and have been limited to radionuclide angiography.⁴² We investigated Doppler parameters of LV ejection and filling dynamics in healthy subjects, patients with single vessel coronary disease and in patients with CAD before and after angioplasty; to assess the changes in Doppler-derived parameters of LV systolic and diastolic function induced by high dose dobutamine-stress and their utility in detection of CAD.

In *chapter 7*. Reproducibility is a major feature of a stress test that needs to be defined when using the test for assessing efficacy of therapeutic interventions. Inter- intra-observer and intertest variability

of dobutamine-atropine echocardiography testing with regard to time of onset of symptoms, hemodynamic parameters, LV wall motion abnormalities and ECG changes are presented in Chapter 7.

In *chapter 8*. The use of the Doppler technique with dobutamine stress, as well as other interventions, is limited by the uncertainty as to whether a change induced by dobutamine is indeed significant or caused by measurement variability. We assessed the reproducibility of Doppler measurements of left ventricular filling during dobutamine stress in normal subjects and patients with CAD and estimated threshold values which can be used as a reference to detect significant changes in Doppler measurements from baseline to peak dobutamine in an individual patient. The results are presented in Chapter 8.

In *chapter 9* the general discussion, summary and conclusions of the studies are presented. The applications of dobutamine stress echocardiography and Doppler in the diagnosis of CAD and assessment of coronary angioplasty; the limitations of the techniques; a review of the literature on the use of stress-Doppler in the evaluation of patients with CAD; and directions for future research are discussed.

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CHAPTER 2

METHODOLOGY

Dobutamine as a Pharmacologic Stress Agent

Dobutamine is a synthetic catecholamine which originally developed as a selective inotropic drug.¹ However, when dobutamine is used in a high dose in patients with coronary artery disease (CAD), myocardial ischaemia may develop.²

Mechanism of action: The effects of dobutamine are mediated by strong β_1 adrenergic receptor stimulation and mild stimulation of β_2 and α_1 receptors.³ The relative inotropic selectivity of dobutamine is mediated by both β_1 and α_1 with β_1 stimulation alone is responsible for its chronotropic effect.⁴ The β_2 mediated vasodilatation and α_1 mediated vasoconstriction effects in the peripheral vasculature are relatively balanced resulting in little net effect on systemic vasculature.²

Haemodynamic responses: The haemodynamic effects of dobutamine correlate linearly with plasma concentration and dose.^{5,6} Intravenous infusion of dobutamine causes an increase in cardiac output mainly through an augmentation of ventricular contractility and a decrease in systemic vascular resistance largely due to reflex withdrawal of sympathetic tone secondary to the increase in cardiac output.¹ Tachycardia and mild increase of systolic pressure usually result when dobutamine is used in a high dose.^{6,7}

The haemodynamic alterations during dobutamine-induced ischaemia involve a decrease in stroke volume with no change in pulmonary wedge pressure.⁶ Dobutamine, as well as other β_1 adrenoceptor agonists, enhances left ventricular (LV) early diastolic distensibility by accelerating relaxation. This is mainly due to the β_1 mediated increase in intracellular cyclic adenosine 3',5'-monophosphate, which accelerates the rate of calcium re-uptake by the sarcoplasmic reticulum and thus stimulating the myocardial deactivation process.^{8,9}

Rationale for the use as a pharmacologic stress agent: The use of dobutamine as an "exercise simulator" for detection of functionally significant coronary stenosis is based on the concept that myocardial ischaemia results from increased myocardial oxygen demand.¹⁰ Dobutamine increases myocardial oxygen demand mainly by increasing heart rate (HR) rather than augmenting contractility.¹¹ Dobutamine-

induced ischaemia may also results from maldistribution of coronary flow between endocardium and epicardium due to coronary vasodilatation.⁷

Dobutamine stress protocol: Specific protocols vary with respect to precise dosage range and the timing of interval stages. Table I shows some of the commonly followed protocols for dobutamine stress testing.

Table I Commonly used protocols for dobutamine stress testing.

	Starting dose ($\mu\text{g/kg/min}$)	Maximum dose ($\mu\text{g/kg/min}$)	Interval stages (min)
Mannering ¹² (1988)	5	20	6-8
Mazeika ¹³ (1992)	5	20	8
Segar ¹⁴ (1992)	5	30	3
Sawada ¹⁵ (1991)	2.5	30	3
Pierard ⁶ (1989)	5	40	5
McNeill ¹⁶ (1992)	10	40*	3

At the Thoraxcentre we modified the dobutamine stress protocol by the addition of atropine.¹⁶ This modification is based on the assumption that addition of atropine to dobutamine causes a significant increase in HR to overcome the poor chronotropic response observed in patients on β blocker therapy.¹⁷

The procedure of dobutamine stress testing presented in this thesis is as follows:

- Baseline recording of 12-lead electrocardiogram (ECG), cuff blood pressure and standard echo views; including parasternal long and short axes and apical four and two chamber views.
- Baseline recordings of Doppler aortic and mitral flow.
- Dobutamine was then administered intravenously using an infusion pump and a graded stress regimen of 10, 20, 30 and 40 $\mu\text{g/kg/minute}$ at 3 minutes stages with the last stage for 6 minutes. Atropine (0.25 - 1 mg) was added, while continuing dobutamine, in patients without signs of ischemia (wall motion abnormalities [WMA], ST-changes or angina) who had not achieved 85% predicted maximum exercise HR during dobutamine alone. During the test the ECG and echocardiogram were continuously monitored. ECG was recorded each minute and cuff blood pressure every 3 minutes. Echo images were recorded on VHS video-tape during the last minute of stages 1 to 3,

and continuously for the last 4 minutes of stage 4 and 10 minutes after discontinuation of infusion. In the Doppler studies, aortic and mitral blood flow were recorded at peak dobutamine infusion.

- Criteria to stop the test were, ST segment depression ≥ 2 mm 80 ms after the J point or ST elevation, severe angina, severe new WMA, significant arrhythmias, achievement of $\geq 85\%$ predicted maximum HR, or any complication regarded as being due to dobutamine.

Side effects: Major side effects during dobutamine stress testing include significant cardiac arrhythmias, hypotension, bradycardia, severe angina pectoris, and less commonly hypertension.^{12-16,18,19} Other minor and less frequent side effects include chills, headache, and anxiety. Recently, we reported the side effects of dobutamine-atropine stress test in 652 examinations.¹⁸ Hypotension, defined as a decrease in systolic blood pressure of >20 mmHg from baseline values, was the most frequent side effect ($n = 34$ examinations). Significant arrhythmias occurred in 24 examinations; one patient had ventricular fibrillation (successfully resuscitated); 3 patients had sustained and 12 non-sustained ventricular tachycardia; and 8 patients had atrial fibrillation or atrial flutter.

Echocardiographic techniques for the evaluation of CAD

Echocardiographic techniques, at rest and during stress, have proven useful for the diagnosis and management of CAD.²⁰ When regional and global as well as systolic and diastolic aspects of LV function are considered, several indicators can be obtained for detection of abnormalities induced by myocardial ischaemia.²¹

Stress echocardiography for assessment of regional myocardial function

The primary purpose of stress echocardiography is to detect transient LV WMA as a result of induced ischaemia. Such abnormalities can vary in degree from hypokinesia, through akinesia, up to dyskinesia.²²

Assessment of regional myocardial function can be achieved by recording and comparing LV wall motion at baseline, during, at peak, and after stress.²³ In this situation, the standard parasternal long and short axis views and the apical four and two chamber views are recorded on videotape or captured digitally in a continuous loop format.²⁴ Cine loop images allow side-by-side display of rest and stress images and images of slightly higher quality.²³ This is particularly useful for exercise echocardiography, where respiratory artifacts interfere with image quality

and minimal acquisition time is mandatory to obtain adequate information. However, digital techniques may be less helpful during pharmacologic stress echocardiography, where image quality is less affected by hyperventilation. In our experience cine loop analysis of dobutamine echocardiography had no advantages for the interpretation of the images over the analysis from video tape.²⁵ Therefore, we did not routinely use a continuous loop format for assessment of dobutamine stress echocardiography.

Regional wall motion can be analyzed using a qualitative, semi-quantitative, or quantitative approach.²⁶ A semi-quantitative analysis can be used by estimating a wall motion score and currently preferable to the existing wall motion quantitation algorithms.²⁶ In our studies, we used a 16-segment LV model.²⁷ Using this approach, each myocardial segment is given a numerical score according to its wall motion as follows²⁷: 1 = normal or hyperkinetic; 2 = hypokinetic; 3 = akinetic; and 4 = dyskinetic. A wall motion score index can then be calculated as the sum of score assigned to each segment divided by the number of segments.²⁸ A score index of 1 implies normal motion in all segments, while higher score imply abnormality.

Interpretation of wall motion analysis: Analysis of regional wall motion can identify the following²⁹⁻³¹: (1) the normal wall motion at rest which becomes hyperkinetic with increased systolic thickening and essentially normal diastolic dimensions in response to stress; (2) evidence of prior infarction with nonviable myocardium, defined as WMA that exist at rest and do not change in response to stress; (3) evidence of viable but dysfunctional myocardium (hibernating or stunned myocardium), defined as WMA that exist at rest but improve in response to a provocative manoeuvre (low-dose dobutamine); and (4) evidence of myocardial ischaemia, defined as the development of new WMA in an area which was normal at rest or worsening of WMA during or at peak stress in a segment which was abnormal at rest.

Doppler assessment of LV systolic function

Pulsed or continuous wave Doppler recordings of the ascending aortic flow may be obtained from the apex, a high right parasternal position, or from the suprasternal notch. The suprasternal approach usually gives the highest velocity in normal subjects and in many patients with a high success rate.³²

For the assessment of LV ejection dynamics using Doppler ultrasound, the ejection phase has been divided into 2 phases:^{33,34}

- *Early active phase:* This phase starts when the aortic valve opens and lasts until the velocity of blood flow in the aorta reaches its peak. During this time, pressure in the LV exceeds pressure in the aorta and blood in the aorta gains momentum.³³ The rate of increase in blood velocity during early systolic ejection is normally constant.³⁴ Events during this phase are influenced mainly by the state of myocardial contractility. This is because the greatest rate of rise in blood velocity (peak acceleration) occurs during the initial 30 to 50 ms of ejection, when the main opposition to LV ejection is inertial, so that the resistive and capacitive properties of the arterial bed have a limited effects.³⁵ Doppler measurements of this phase include (Figure 1):³⁶⁻³⁸ (a) acceleration time (AT), defined as the time interval from the onset of ejection to the point of peak aortic velocity; (b) peak aortic velocity, which is determined as the midpoint of the Doppler flow spectrum at the time of maximum flow velocity; and (c) average aortic acceleration; which is calculated by dividing the peak flow velocity by the acceleration time.

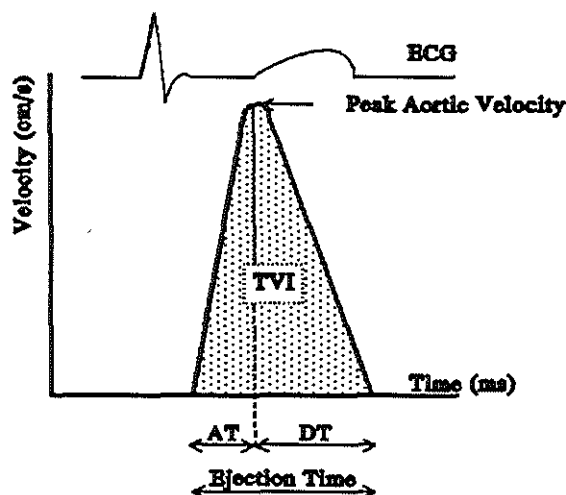


Figure 1: Schematic representation of Doppler aortic velocity profile, showing measurements which can be obtained. AT = acceleration time, DT = deceleration time, PEP = pre-ejection period, TVI = systolic time velocity integral.

- *Latter, more passive, LV ejection:* This phase starts at a point when blood velocity reaches its peak and lasts until the momentum of the blood falls to zero.³³ During this phase LV volume decreases and the long axis of the LV shortens. In fact, the LV is supporting the aortic pressure at this time, maintaining, rather than actively generating a force. The blood has enough momentum from the active phase to complete the normal ejection. Unlike the early active phase, the duration of the second phase varies with the state of the arterial bed.^{33,34} Doppler measurements of this phase include (Figure 1):^{36,37}

(a) deceleration time (DT), defined as the time interval from the point of peak aortic velocity to the end of systolic ejection; (b) average aortic deceleration, which is calculated by dividing the peak aortic velocity by the deceleration time.

The systolic time velocity integral (TVI) represents the Doppler index of stroke volume. It is measured as the area under the aortic velocity signal and represents the forward distance travelled by the blood during the ejection phase (Figure 1).³⁶

Factors influencing Doppler ejection variables

(1) *Effect of the inotropic state:* Peak aortic velocity and peak or average aortic acceleration are reliable measures of LV contractility.³⁸ Initial studies suggested that peak velocity and in particular the maximal acceleration of blood flow in the ascending aorta are sensitive indicators of the inotropic state and relatively insensitive to the loading conditions of the heart.^{39,40} This is confirmed by subsequent studies, using electromagnetic velocity catheters,⁴¹ and more recently using Doppler-echocardiography.^{13,36,42,43}

(2) *Effect of myocardial ischaemia:* Data from animal studies demonstrated that in the presence of critical coronary stenosis Doppler indices of LV function, specifically peak acceleration, fail to increase during conditions which increase myocardial oxygen requirements (isoproterenol) to levels reached in the absence of such stenosis.⁴⁴ In addition, the percent reduction of peak acceleration has been shown to correlate best with the percent ischaemic mass at risk, followed by ejection fraction, TVI and peak velocity.⁴⁵ The results of these animal studies and other clinical studies,^{37,46} encouraged combining Doppler examination of global LV systolic function, with cardiac stress testing for the detection of significant CAD.

(3) *Effect of abrupt coronary occlusion:* Balloon inflation during coronary angioplasty, in patients without collaterals, has been shown to significantly reduce ejection indices derived by continuous wave Doppler.⁴⁷ Whereas, in patients with collaterals coronary flow, ejection indices may remain unchanged during coronary occlusion.⁴⁷

(4) *Effect of myocardial infarction:* Doppler measurement of velocity based indices of LV systolic function during acute myocardial infarction demonstrated: (a) a significantly lower peak velocity, maximal acceleration and TVI in patients with acute infarction than their age-matched healthy subjects;³⁷ (b) a marked improvement in LV function, based on serial measurements of peak aortic acceleration, in patients with a first myocardial infarction not complicated by heart failure and no significant recovery in patients with a previous infarction or those with a first infarction complicated by heart failure.⁴⁸

(5) *Effects of β -blockade and β -stimulation:* Administration of a β -adrenergic blocking agent causes a smaller rise in peak ejection velocity and mean acceleration with exercise in normal subjects compared to a drug free state.⁴⁹ β -stimulation using dobutamine 5 $\mu\text{g/kg/min}$ in normal subjects results in significant increase in maximal aortic acceleration with minimal increase in stroke volume.⁵⁰

(6) *Effects of preload, afterload, HR and body position:* Increased afterload, by controlled infusion of methoxamine, while maintaining constant HR, by means of transoesophageal pacing, in normal subjects, significantly reduces peak aortic velocity and acceleration with no change in TVI.⁵¹ On the other hand, reduced afterload, by administration of nitroprusside, while maintaining preload, by infusion of saline, in CAD patients, results in a significant increase in Doppler ejection indices, while administration of saline alone results in no significant increase in the three parameters.⁵²

Alterations in HR, results in a consistent inverse linear relation between HR and Doppler-derived average aortic acceleration, peak velocity and TVI in normal subjects.⁵³ Finally, it has been noted that changing the subject position from the supine to the upright position results in a decline in Doppler variables of aortic flow.^{53,54}

(7) *Effects of age, gender and body surface area:* Doppler-derived aortic ejection parameters have been shown to decrease progressively with age

either at rest or during exercise in normal subjects.^{55,56} No significant relationship has been found between body surface area and normal resting Doppler aortic flow measurements.⁵⁵ The impact of gender on Doppler ejection indices is rather controversial. Lazarus et al⁵⁶ demonstrated that gender did not affect Doppler aortic indices, either at rest or during exercise, in normal subjects. In contrast, Mowat et al⁵⁷ reported that aortic peak velocity and acceleration are significantly higher in males than in females.

Doppler Assessment of LV diastolic function

The transmitral flow velocity pattern reflects the changing diastolic pressure differences between the LV and the left atrium.⁵⁸ The use of Doppler techniques for the detection of LV filling abnormalities is based on: (1) defining normal Doppler velocities and patterns, and understanding how these velocities relate to filling characteristics of the LV;^{58,59-63} (2) understanding the determinants of LV diastolic filling patterns;^{58,60,64,65} (3) understanding the influence of factors such as HR, loading condition, age and drugs on LV filling patterns;^{9,68,69} and (4) understanding the natural history of LV filling abnormalities in cardiac disease states and how the Doppler velocity patterns relate to patient symptoms, and haemodynamics.^{60,66,67}

Normal transmitral flow pattern

For the assessment of diastolic function, the diastolic period has been divided into four phases beginning with aortic valve closure and ending with mitral valve closure.^{60,67}

- *Isovolumic relaxation*: No filling occurs during this phase, however, processes that determine the rate of fall of isovolumic pressure may influence ventricular filling following mitral valve opening.⁷⁰ It is usually assessed by measuring the isovolumic relaxation period (IRP) as the time from aortic valve closure detected by phonocardiography or Doppler to mitral valve opening (Figure 2). Events during this phase are attributed primarily to myocardial relaxation.⁶⁰
- *Rapid LV filling*: This phase extends from the onset of mitral flow to the point where LV filling plateaus. The onset of flow begins when the LV pressure drops below the left atrial pressure. At this point the blood within the mitral apparatus is subjected to a growing force generated by the atrioventricular pressure gradient, which causes the

blood to accelerate.⁶² The acceleration time (AT) for early filling is the time interval from mitral valve opening to peak early filling velocity (Figure 2). During this period, the LV pressure decreases more rapidly than the left atrial pressure due to progressive active myocardial relaxation and diastolic suction of the LV creating a pressure gradient between the left atrium and the LV.⁷¹ This gradient produces a high initial peak velocity (E) due to rapid forward filling⁶⁰ (Figure 2). When LV relaxation nears completion, the transmitral velocity decelerates.⁷² The rate of decline in the mitral velocity can be measured by the deceleration time (DT), which is the time interval from peak E to an extrapolation of the deceleration slope to the baseline (Figure 2).⁶⁰

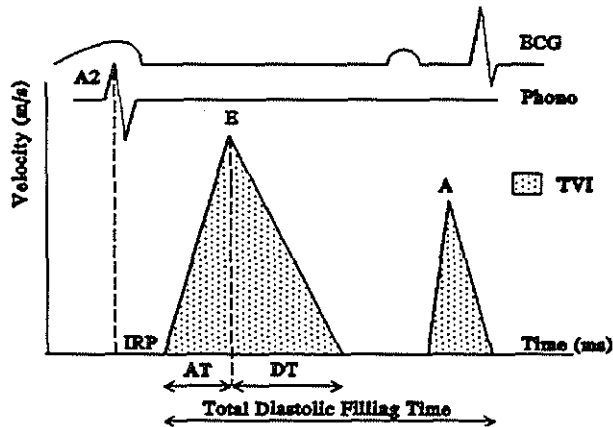


Figure 2: Schematic representation of transmitral velocity profile, demonstrating Doppler measurements of LV filling. A = peak atrial filling; A2 = aortic component of second heart sound; AT = acceleration time, DT = deceleration time; E = peak early filling velocity; IRP = isovolumic relaxation period; TVI = diastolic time velocity integral.

- *Slow filling phase "diastasis"*: During this phase the left atrial and LV pressures are nearly equilibrated and only the blood returning from the lungs flows through the left atrium into the LV.⁷² This results in continued low velocity forward flow. This phase is felt to be related to LV compliance.⁶²

- *Atrial contraction:* During this phase the atrial pressure increases producing a left atrial-to-LV pressure gradient that propels blood into the LV with the resultant second peak (A) velocity⁶⁶ (Figure 2). In addition to atrial contractile force, this phase is felt to be the portion of diastole that may be most modified by LV stiffness and pericardial restraint.⁶⁷

Factors determining diastolic filling of the LV

In general, factors that determine LV filling will influence the Doppler transmitral velocity profile.⁶³ Despite the fact that a multitude of factors affect LV filling, it appears that they all act through their influence on the transmitral pressure gradient.⁶⁶ These factors include:^{63,64,73}

Myocardial relaxation and elastic properties

- Regional myocardial relaxation
- Nonuniformity of regional myocardial relaxation in time and space
- Diastolic suction: elastic recoil or inertial properties

Chamber stiffness or compliance

Passive properties

- Ventricular geometry: size, shape and wall thickness
- Composition of ventricular wall: muscle, connective tissue (amount, type, and configuration), amyloid, haemosiderin, oedema.

Dynamic properties:

- Viscoelastic myocardial properties
- External forces: pericardial constraints, right ventricular loading, lung pressure, and tumours

Left atrial pressure

Other factors

- HR and rhythm
- Age, gender and body surface area
- Loading conditions
- Technical factors: sample volume position and respiration

(1) *Myocardial relaxation:* Myocardial relaxation is an active energy-requiring process, in which calcium is sequestered by the sarcoplasmic reticulum with the consequent dissociation of actin-myosin crossbridges.⁷⁰ It starts before aortic valve closure, lasts throughout and influences early filling and usually ends by the middle of diastole and thus does not

normally affect diastasis or atrial filling.⁶¹ The rate of LV relaxation is inversely related to the peak rate of LV filling.^{60,65} Thus, faster relaxation increases early filling with consequent increase in mitral E wave velocity, while slower relaxation results in a decrease in atrioventricular pressure gradient and lower E wave velocity.^{58,60,65,74}

Factors that accelerate myocardial relaxation includes increased HR and catecholamines.^{9,75} Whereas factors that slow myocardial relaxation include advanced age, myocardial ischaemia, LV hypertrophy, dilated cardiomyopathy, hypothyroidism and intracellular calcium overload.^{60,61}

Nonuniformity of relaxation may influence any of the parameters of LV filling. Normally, the rate of relaxation of the different LV segments is variable. This variability may be exaggerated under different disease states and may affect the mitral velocity profile.⁶⁰

Experimental studies,^{75,76} supported the concept of diastolic suction of blood from the atria to fill the ventricles as an action caused by elastic recoil or by inertial properties of the myocardium.

(2) *LV chamber stiffness or compliance:* Chamber stiffness is a function of both myocardial stiffness and the thickness and geometry of the ventricle.⁵⁹ LV chamber stiffness is variable during the rapid filling of early diastole, low during diastasis and increasing steadily as LV filling becomes complete during late diastole.⁶⁴ LV chamber stiffness is proportional to LV diastolic pressure. Increased chamber stiffness results in an increase in left atrial pressure and a high mitral opening pressure causing increased early filling velocity and shortened IRP.⁶⁷ The nondistensible LV also produces a rapid equilibration of left atrial and LV pressures and reduced atrial transport. This will result in a short DT and a decreased A velocity, respectively.^{62,67}

Increased LV stiffness has been demonstrated in conditions associated with marked ventricular hypertrophy;^{64,78} and in patients with altered composition of LV wall such as those with myocardial scar after myocardial infarction,⁷⁹ chronic CAD and scattered myocardial fibrosis,⁸⁰ or restrictive cardiomyopathies.⁶⁴

Viscosity of elements within ventricular wall represents a resistance to filling that is proportional to the rate of filling.⁶¹ The viscous effects will be enhanced, if a given diastolic volume is rapidly entered into the ventricle, resulting in greater wall force and chamber pressure rise.⁶⁴

The pericardium, right ventricle and lungs are structures that surround the heart and constitute the external constraints of the LV.⁶¹ The distending pressure of the LV is the difference between the internal

and external pressure.⁸¹ An elevated pericardial pressure or right ventricular volume will result in restriction of LV filling.⁸²

(3) *Left atrial pressure:* Left atrial pressure is a major determinant of transmitral pressure gradient.⁵⁸ It is determined by the interaction of several factors including, left atrial contractility and its timing, left atrial compliance, left atrial volume and LV chamber stiffness.⁶³ Reduction in left atrial pressure will result in a decrease in transmitral pressure gradient and consequently a reduced early filling velocities.⁶⁰ While an increase in left atrial pressure will result in a higher driving pressure across the mitral valve with subsequent increase in early filling velocities.⁶⁶ In presence of increased HR or prolongation of the PR interval, atrial systole may occur during the deceleration slope of early filling resulting in its reduction and increase in atrial filling velocity.⁶³

(4) *Interaction of myocardial relaxation, chamber stiffness, and left atrial pressure:* Coexistence of reduced relaxation and increased left atrial pressure, due either to increased chamber stiffness or abnormalities in loading conditions, results in contrasting effects on LV diastolic filling.⁶⁶ Thus, the presence of equally significant impaired relaxation and increased stiffness may maintain the balance between early and late diastolic filling, causing the mitral velocity profile to undergo "pseudonormalization".^{63,66}

(5) *Heart rate and rhythm:* Experimental and clinical studies⁸³⁻⁸⁵ demonstrated that, increasing HR significantly increases atrial contribution to filling with no significant change in early filling. The presence of arrhythmias such as atrial fibrillation or multiple ventricular ectopic beats complicates the interpretation of LV filling pattern. Abnormal electrical activation of the LV (such as bundle branch block) slows LV relaxation.⁸⁶ In patients with atrioventricular dissociation, the mitral velocity will vary according to the timing of atrial contraction.⁶⁰

(6) *Age, gender and body surface area:* With increasing age, LV early filling gradually decreases with gradual increase in filling during atrial contraction.⁶⁶ Progressive slowing of relaxation has been suggested as the primary underlying mechanism. Advancing age may also increase myocardial stiffness due to increase LV mass.⁸⁷ This would increase the E/A ratio and not reduce it as is commonly observed in aging. Recently, Davidson⁸⁸ suggested that increased viscoelasticity of the ventricle with

aging could be an alternative hypothesis. Doppler findings may show lengthening of the IRP and DT, a reduction in peak E velocity, an increase in peak A velocity and a decrease in the E/A velocity ratio to approximately one.^{69,89,90} Several studies^{69,89} showed no significant relation between Doppler parameters of LV filling and either body surface area or gender.

(7) *Loading conditions:* Changes in preload influence the LV filling pattern through their effect on left atrial pressure.^{62,66} With increased preload, there will be a higher left atrial pressure relative to LV pressure in early diastole.⁷⁵ This results in a transmitral velocity profile similar to that of restricted LV filling.⁵⁸ Conversely, a decrease in preload results in a lower initial pressure gradient and consequently the Doppler pattern may simulate that of impaired LV relaxation.⁶⁰

Acute elevations of blood pressure in healthy subjects had no independent effect on the Doppler indices of LV filling.^{68,91} However, chronic volume overload, e.g., severe aortic regurgitation, increases LV early diastolic pressure resulting in rapid equalization of left atrial and LV pressures and the DT will be shortened.⁹² Severe mitral regurgitation causes a high initial pressure gradient across the mitral valve and results in a high E wave velocity.⁹² However, the presence of trivial mitral regurgitation probably does not affect the transmitral velocity profile.⁶⁰

(8) *Respiration:* During inspiration there is a decrease in LV filling velocities.⁹³ The effects of respiration can be minimized by acquiring Doppler data during periods of apnoea or by averaging multiple consecutive beats.

(9) *Sample volume position:* When obtaining mitral flow velocity recordings, the position of the sample volume should be standardized. Placing the sample volume at the level of the mitral valve annulus has the advantage of less change in cross-sectional area,⁶⁰ but yields a lower early filling velocity and shorter deceleration time than sampling at the tips of the mitral leaflets.^{94,95} Conversely, the mitral leaflet tip site yields the highest velocity change and most discrete signals, although the cross-sectional area varies throughout diastole.⁵⁸ Since flow velocities are closely related to the left atrial-LV pressure gradient and pressure gradient is the major determinant of transvalvular flow, the velocities recorded at the leaflet tips are generally accepted as the best indirect measure of the driving force across the mitral valve.^{60,66}

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CHAPTER 3

ENHANCED SENSITIVITY FOR DETECTION OF CORONARY ARTERY DISEASE BY ADDITION OF ATROPINE TO DOBUTAMINE STRESS ECHOCARDIOGRAPHY¹

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Abstract

Patients undergoing dobutamine stress echocardiography are often using beta antagonists which limit heart rate response and sensitivity of the test for detection of coronary artery disease. The aim of this study was to assess the effect of addition of atropine to dobutamine on clinical, electrocardiographic and echocardiographic outcomes.

Dobutamine echocardiography was performed starting at and increasing every 3 minutes by 10 $\mu\text{g/kg/min}$ to a maximum of 40 $\mu\text{g/kg/min}$ (stage 4) which was continued for 6 minutes. In patients not achieving 85% predicted maximal exercise heart rate and in whom the test was not judged to positive on echocardiographic or ECG criteria, atropine was added starting at a dose of 0.25 mg intravenously and repeated if necessary to achieve an adequate heart rate or until the test was stopped because of chest pain or ECG changes.

Of 80 consecutive patients undergoing dobutamine echocardiography within 2 weeks of coronary angiography, 49 required atropine (group A) and 31 required only dobutamine (group B). After dobutamine alone,

¹Am J Cardiol 1992;70:41-46

mean \pm SD heart rate was higher in group B than in group A: 129 ± 20.1 compared with 90 ± 18.4 , $p < 0.0001$, but after addition of atropine, heart rate in group A increased to 120 ± 19.6 . Overall sensitivity for the detection of coronary disease was 70%; after addition of atropine, sensitivity for group A was 65% and in group B, sensitivity was 81%. Overall specificity for detection of coronary disease was 88%; specificity was 89% after atropine in group A and 87% in group B. There were no severe complications and no difference between groups in the frequency of complications or the requirement of beta blocker for relief of symptoms.

The addition of atropine to DSE in patients in whom the test is negative and who do not achieve 85% predicted maximal heart rate during dobutamine alone, increases the sensitivity of the test for detection of coronary artery disease without loss of specificity and without severe side effects.

Introduction

Stress echocardiography with exercise has a high sensitivity, specificity and reproducibility^{1,2} for non-invasive detection of coronary artery disease but requires adequate cooperation and motivation; this may be impossible in patients with orthopaedic or neurological conditions that preclude exercise. An alternative is to combine echocardiography with pharmacological stress with dobutamine³, dipyridamole⁴, or adenosine⁵.

Dobutamine is a sympathomimetic agent with both positive chronotropic and inotropic effects⁶, which in high dose increases myocardial oxygen demands inducing myocardial ischaemia in the presence of significant coronary stenoses. Comparison of dobutamine stress echocardiography and exercise electrocardiography in patients taking β antagonists shows lower mean peak heart rate and systolic blood pressure during dobutamine than during exercise.³ We postulated that this relatively low peak heart rate during dobutamine stress may adversely affect the sensitivity of dobutamine stress echocardiography. Accordingly, we altered the protocol for dobutamine stress echocardiography to incorporate the addition of atropine at the end of the usual dobutamine infusion in patients not achieving 85% predicted maximal exercise heart rate, and in whom the stress test was not regarded as positive during dobutamine alone. The aim of the study was to assess the effect of the addition of atropine to dobutamine on clinical, electrocardiographic and echocardiographic outcomes of the stress test, and to assess the sensitivity

and specificity of this combined pharmacologic stress test for detecting coronary artery disease.

Methods

Patient selection: Patients who received atropine in this study formed a subgroup of consecutive patients undergoing dobutamine stress echocardiography who (1) also underwent coronary angiography within 2 weeks of stress testing; (2) had negative results after dobutamine stress echocardiography with administration of dobutamine alone; and (3) did not achieve 85% predicted maximal exercise-induced heart rate for age and sex during dobutamine alone.

Stress echocardiography (Figure 1): After informed verbal consent, 2-dimensional precordial echocardiography was performed at rest using Hewlett-Packard Sonos 1000 echo apparatus with 2.5 and 3.5MHz transducers. Standard apical and parasternal views were recorded on video tape. The optimal transducer positions were marked on the chest and baseline 12-lead electrocardiogram performed. When the standard position of a chest electrode coincided with the marked transducer position the electrode was moved one space higher or lower.

After baseline 12-lead electrocardiogram, dobutamine infusion was administered intravenously using an infusion pump, starting at a dose of 10 mcg/kg/minute for 3 minutes, and increasing by 10 mcg/kg/min every 3 minutes to a maximum of 40 mcg/kg/minute (stage 4); this was continued for 6 minutes. In patients not achieving 85% predicted maximal exercise heart rate, atropine (0.25 mg) was given intravenously at the end of stage 4, and repeated to a maximum of 1 mg if necessary with the continuation of dobutamine for up to a further 5 minutes if necessary to achieve 85% predicted maximum exercise heart rate.

Throughout dobutamine infusion the electrocardiogram was continuously monitored, 12-lead electrocardiogram recorded each minute and cuff blood pressure taken every 3 minutes. Two-dimensional echocardiography was continuously monitored; standard parasternal and apical images were acquired by one of the authors and were recorded on videotape for the last minute of each of stages 1 to 3, the last 4 minutes of stage 4 and continuously for up to 5 minutes after atropine administration. The infusion was stopped if the patient developed obvious new wall motion abnormality, ST depression of >2 mm 80 ms after the J point, ST elevation, significant chest pain, ventricular tachycardia, a decrease in blood pressure >20 mm Hg from resting value or any complication

considered to be due to dobutamine. Metoprolol was available and used to reverse the effects of dobutamine or atropine if these did not revert spontaneously and quickly.

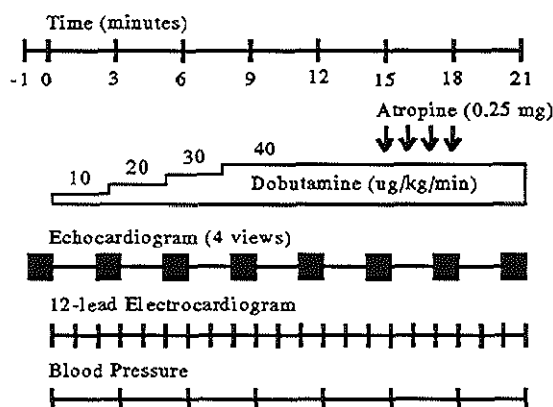


Figure 1. Schematic representation of the study protocol.

Echocardiographic assessment: In addition to assessment of echo images during acquisition, additional assessment was also performed by 2 experienced investigators following acquisition. Both on- and off-line assessments were done without knowledge of the patients' coronary anatomy but with knowledge of the doses of dobutamine and atropine used. When there was disagreement between the 2 off-line assessors, a third investigator viewed the images without knowledge of the previous assessments and a majority decision was achieved. For this semiquantitative assessment the left ventricular wall was divided into 16 segments⁷ and scored using a 4 point scale: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. An increase in score between rest and stress in 1 or more segments, i.e., a new or worsened wall motion abnormality, constituted a positive test. Using this system an index of global left ventricular wall motion (wall motion score index) was calculated as sum of the scores in the visualized segments/number of segments visualized; indexes were derived for images acquired at baseline, peak dobutamine and after atropine. In our laboratory inter- and intra-observer agreement for stress echocardiographic assessment is 91%;⁸ recent data indicate that assessment of 100 stress echocardiograms is

adequate training for diagnostic accuracy in this technique⁹ and all investigators in our center have such experience. We do not routinely use a continuous loop format for assessment of pharmacological stress echocardiography because we previously tested if cine loop analysis of dobutamine echocardiography had advantages over analysis of images from video tape and found the same results by the 2 techniques³.

Coronary angiography: Coronary angiography was performed by the Judkins' technique within 2 weeks of stress echocardiography. A lesion of >50% diameter stenosis is taken as representing significant coronary artery disease. The decision to perform coronary angiography was never based on the results of stress echocardiography.

Statistical analysis: Results are expressed as mean \pm SD and 95% confidence intervals (CI) are given where appropriate. Discrete variables were compared using the chi-square test or Fisher's exact test; continuous variables were compared using paired and unpaired Student's *t* tests or 1 way analysis of variance as appropriate.

Results

Study population: Eighty consecutive patients undergoing dobutamine stress echocardiography and coronary angiography were included in the study. Clinical details are summarised in Table I. Forty-nine patients received atropine in addition to dobutamine (group A) and 31 achieved a test end point with dobutamine alone (group B). There was no difference between these 2 groups with regard to the overall incidence of significant coronary artery disease, but there was a trend toward more 1-vessel disease in group A: 24 of 31 (77%) patients with coronary disease in group A had 1-vessel disease compared with 8 of 16 (50%) in group B, *p* = 0.11. The distribution of diseased vessels was different between the 2 groups, with a greater proportion of patients from group A having left anterior descending and circumflex lesions and more patients in group B having right coronary lesions. Mean age was lower and β antagonist use was more frequent in group A. There was no difference between groups in the frequency of previous infarction, angioplasty or coronary artery bypass grafting.

Reasons for termination of the test: The primary reasons for termination of the stress test in the 2 groups are listed in Table II. In some cases a patient had an additional reason for stopping, e.g. chest pain accompanying ST elevation. There was no difference between groups in the reasons for termination of the test; in >60% of patients from both

groups, the test was discontinued primarily because an adequate heart rate was achieved. In only 1 patient was the test stopped because of new wall motion abnormality.

Table I. Clinical characteristics of patients receiving atropine (group A) and no atropine (group B).

	Group A	Group B	p Value
No. of patients	49	31	
Men:women	40:9	19:12	0.08
Mean age \pm SD	57 \pm 12	62 \pm 10	0.05
Coronary artery disease	31 (63%)	16 (52%)	NS
1-vessel:multivessel	24:7	8:8	0.11
LAD:LC:right	21:12:7	8:5:11	0.05
Previous MI	19 (39%)	9 (29%)	NS
Previous PTCA	24 (49%)	15 (48%)	NS
Previous CABG	2 (4%)	2 (7%)	NS
β antagonists	46 (94%)	18 (58%)	0.0003
Calcium antagonist	29 (59%)	15 (48%)	NS
Nitrates	20 (41%)	13 (42%)	NS
CABG = coronary artery bypass grafting, LAD = left anterior descending, LC = left circumflex, MI = myocardial infarction, NS = not statistically significant, PTCA = percutaneous transluminal coronary angioplasty.			

Table II. Frequency of primary reasons for stopping stress test.

	Group A	Group B
No. of patients	49	31
Adequate heart rate	30 (61%)	19 (61%)
Chest Pain	12 (25%)	7 (23%)
ST elevation	2 (4%)	4 (13%)
ST depression	3 (6%)	0
New wall motion abnormality	0	1 (3%)
Chills	2 (4%)	0

Hemodynamic changes: Changes in heart rate and systolic blood pressure with dobutamine and atropine are shown in Tables III and IV. In group A, both heart rate and systolic blood pressure increased significantly after dobutamine alone and increased further after addition of atropine. Within group A there was no difference between patients with and without coronary artery disease for either mean heart rate or systolic blood pressure at baseline, after dobutamine or after addition of atropine. In

group B, mean heart rate and systolic blood pressure increased significantly from baseline to peak dobutamine, and there was no difference between those with and without coronary artery disease for values at base and peak stress.

Comparison of heart rate data between groups A and B showed a higher baseline value in group B: 76 ± 13.6 beats/min compared with 64 ± 9.6 beats/min, $p < 0.0001$. At peak dobutamine, heart rate in group A was 90 ± 18.4 beats/min compared with 129 ± 20.1 beats/min in group B, $p < 0.0001$. There was a small difference between peak stress (peak atropine in group A, peak dobutamine in group B) heart rates in the 2 groups: 120 ± 19.6 beats/min for group A and 129 ± 20.1 beats/min for group B, $p = 0.04$.

Table III. Changes in heart rate after dobutamine and atropine.

	Base	Peak Dobutamine	Peak Atropine	p Value
Group A (all)	64 ± 9.6	90 ± 18.4	120 ± 19.6	<0.0001
(+CAD)	63 ± 9.8	88 ± 18.7	118 ± 19.0	<0.0001
(-CAD)	66 ± 9.7	92 ± 18.3	122 ± 20.0	<0.0001
Group B (all)	76 ± 13.6	129 ± 20.1		<0.0001
(+CAD)	74 ± 14.6	128 ± 21.4		<0.0001
(-CAD)	77 ± 12.8	130 ± 19.3		<0.0001
Analysis in group A was performed by 1-way analysis of variance and in group B by paired <i>t</i> tests. +CAD = patients with significant coronary artery disease, -CAD = patients without significant coronary artery disease.				

Table IV. Changes in systolic blood pressure after dobutamine and atropine.

	Base	Peak Dobutamine	Peak Atropine	p Value
Group A (all)	129 ± 17	139 ± 19	147 ± 24	<0.0001
(+CAD)	127 ± 16	140 ± 19	149 ± 25	<0.0003
(-CAD)	131 ± 19	139 ± 18	142 ± 23	0.25
Group B (all)	136 ± 22	148 ± 30		0.001
(+CAD)	142 ± 25	154 ± 33		0.03
(-CAD)	130 ± 17	141 ± 25		0.01
Explanation and abbreviations as Table III.				

Base and peak dobutamine systolic blood pressures tended to be higher in group B although the differences did not reach statistical significance: 129 ± 17 mm Hg compared with 136 ± 22 mm Hg, $p = 0.09$ for baseline values, and 139 ± 19 mm Hg compared with 148 ± 30 mm Hg, $p = 0.13$ for peak dobutamine. There was no difference between groups A and B for peak stress systolic blood pressure: 147 ± 24 mm Hg and 148 ± 30 mm Hg, $p = 0.86$.

Sensitivity and specificity of stress echocardiography: Of the 47 patients with significant coronary artery disease, 33 developed a new or worsened wall motion abnormality in the area of myocardium judged to be subtended by the stenotic coronary artery after either dobutamine or atropine (an overall sensitivity of 70%, 95%CI 55 to 83%). In group A, off-line review revealed new wall motion abnormalities which had been unrecognised during on-line assessment in 2 of 31 (7%, 95%CI 1 to 21%) patients with coronary artery disease before addition of atropine, and 20 of 31 had new wall motion abnormalities after addition of atropine (sensitivity for group A of 65%, 95%CI 45 to 81%). In group B, new or worsened wall motion abnormalities occurred in 13 of 16 patients with coronary artery disease (sensitivity of 81%, 95%CI 54 to 96%) (Figure 2).

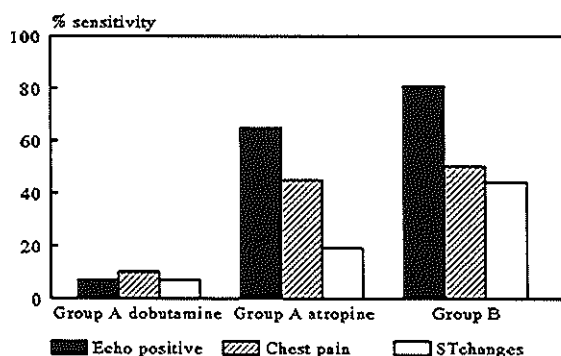


Figure 2. Sensitivity of echocardiography (Echo), chest pain and ST segment changes for detection of coronary artery disease. Group A atropine = sensitivities after addition of atropine; Group A dobutamine = sensitivities in group A before addition of atropine.

The overall specificity of stress echocardiography for detection of coronary artery disease was 88%, 95%CI 72 to 97% (4 of 33 patients without significant coronary disease developed a new or worsened wall motion abnormality after either dobutamine or atropine). In group A, none of the 18 patients without coronary disease had a positive echo with dobutamine alone, but in 2 patients the echo became positive after addition of atropine (specificity of 89%, 95%CI 65 to 99%). In group B, 2 of the 15 patients without coronary disease had a positive echocardiographic results after dobutamine (specificity of 87%, 95%CI 60 to 98%) (Figure 3).

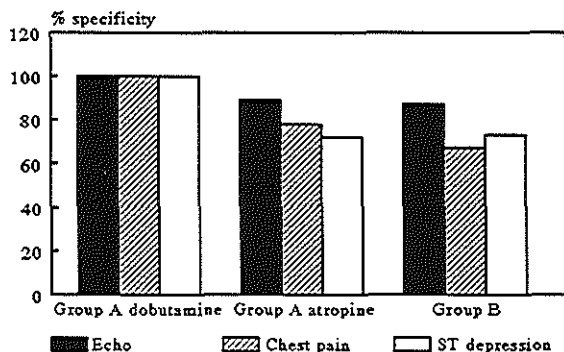


Figure 3. Specificity of echocardiography (Echo), chest pain and ST depression for detection of coronary artery disease. Group A atropine = specificities after addition of atropine; Group A dobutamine = specificities in group A before addition of atropine.

Sensitivity and specificity of ST changes and chest pain: Sensitivities of ST changes and chest pain induced by dobutamine or atropine as indicators of coronary artery disease are also shown in Figure 1. In group A, 2 of 31 patients (7%, 95%CI 1 to 21%) with coronary disease had ST depression of 1 mm 80 ms after the J point during dobutamine alone, while 6 (19%, 95%CI 8 to 38%) had ST changes (4 depression, 2 elevation) after addition of atropine. In group B, 7 of 16 patients (44%, 95%CI 20 to 70%) with coronary disease had ST changes (4 elevation) during administration

of dobutamine. In the 6 studies that resulted in ST elevation, this quickly resolved on termination of the stress test and administration of intravenous metoprolol. Three of these patients had previous infarction and 1 had a totally blocked right coronary artery despite no history of infarction; 3 had multivessel and 3 single vessel disease.

Of 31 patients with coronary artery disease in group A, chest pain occurred in 3 (10%, 95%CI 2 to 26%) during dobutamine alone, and in 14 (45%, 95%CI 27 to 64%) after addition of atropine. In group B, 8 of 16 patients (50%, 95%CI 25 to 75%) with coronary artery disease had chest pain during dobutamine therapy.

Specificities of dobutamine- and atropine-induced ST segment changes and chest pain for detection of coronary artery disease are shown in Figure 3. There was no ST depression or chest pain in the 18 patients without coronary disease in group A during dobutamine therapy alone, but ST depression occurred in 5 patients (specificity 72%, 95%CI 47 to 90%) and chest pain in 4 (specificity 78%, 95%CI 52 to 94%) after addition of atropine. In group B, 4 of the 15 patients without coronary disease developed ST depression during dobutamine therapy, (specificity 73%, 95%CI 45 to 92%), and 5 experienced chest pain (specificity 67%, 95%CI 38 to 88%).

Table V. Side effects at peak stress during dobutamine or atropine.

	Group A	Group B
Continuing chest pain	10	11
Ventricular tachycardia (3 beats)	2	1
Atrial ectopics	1	0
Nodal rhythm	1	0
Chills	2	1
Headache	1	0
Dyspnea	0	1

Wall motion score indexes: There was no change in mean wall motion score index between rest and peak dobutamine (1.04 ± 0.13 compared with 1.06 ± 0.14 , $p = 0.21$) in patients with coronary artery disease in group A, but there was a significant increase in mean wall motion score index between peak dobutamine and peak atropine (1.06 ± 0.14 to 1.17 ± 0.15), $p < 0.0001$. Mean wall motion score index for patients with coronary artery disease in group B increased from 1.29 ± 0.42 at baseline to 1.52 ± 0.43 after dobutamine, $p < 0.0001$. There was no change in wall motion score index for patients without coronary disease in either group A or group B.

Complications: There were no serious complications related to either dobutamine or atropine. One or more minor side effects occurred at peak stress in 15 patients from group A (31%) and 13 patients (42%) from group B (Table V); 11 patients (23%) from group A and 12 (39%) from group B required intravenous metoprolol after peak stress, usually for relief of chest pain which did not settle quickly and spontaneously. There was no significant difference between groups in the incidence of side effects or requirement for metoprolol (Table V).

Discussion

Study Rationale: Patients undergoing non-invasive cardiac investigations at our institution are often receiving beta antagonists^{3,8} for suspected angina, after infarction or for hypertension, and withdrawal of medication may be impractical or even potentially hazardous. Dobutamine has beta stimulant properties⁷ that result mainly in increased inotropic and, to a lesser extent, increased chronotropic effects that are reduced in patients using β blockers. We postulated that this may limit the sensitivity of dobutamine stress testing for detection of coronary artery disease in these patients. Our suspicions were supported by data from other centers that showed a high incidence of electrocardiographic changes^{10,11} during dobutamine infusion in patients with coronary disease who are not taking β antagonists, and by recent data that indicate that antianginal therapy including β blockade limits the sensitivity of dipyridamole echocardiography¹².

The negative chronotropic effect of β antagonists can be overcome by atrial pacing, which is an alternative nonexercise stress; however, even by the oesophageal route¹³ this requires adequate patient cooperation and suitable pacing electrodes and has no effect on inotropic action. Therefore, to retain the inotropic effect of dobutamine, but to overcome the lack of chronotropic effect seen especially in patients receiving β antagonists, we combined dobutamine stress echocardiography with the addition of atropine to increase heart rate¹⁴ in patients with negative stress echocardiography who did not achieve 85% predicted maximal exercise-induced heart rate with dobutamine alone. We compared the results of this combined stress test with those seen in the same patients after dobutamine alone, and with the outcome of stress echocardiography in consecutive patients undergoing dobutamine stress testing without the requirement for atropine, during the same time period as those who received atropine.

Stress echocardiography: sensitivity, specificity, and wall motion score index: In accordance with the protocol, no patient with a positive echocardiogram during dobutamine therapy alone should have received atropine. However off-line review revealed minor new wall motion abnormalities which had not been detected on-line before addition of atropine to 2 patients from group A. The sensitivity for detection of coronary lesions with >50% diameter stenosis was 65% for patients in group A, and 81% for group B, resulting in an overall sensitivity of 70%, with very similar CIs for groups A and B; this similar sensitivity was achieved despite a tendency towards more multivessel disease in group B, a factor which we have previously shown to increase positivity of dobutamine stress echocardiography³. Had these patients been studied using our former protocol, stopping after 15 minutes dobutamine infusion regardless of heart rate, 15 of the 47 patients with coronary disease would have had a positive echocardiogram, resulting in a significantly lower sensitivity of 32%, 95%CI 19 to 47%.

The overall sensitivity for detection of coronary disease of 70% with a 95% CI of 55 to 83% is slightly lower but comparable to that reported for tomographic thallium scintigraphy after exercise⁵ or pharmacologic stress with adenosine⁵ or dipyridamole¹⁵; however, our study of patients with predominantly 1-vessel disease cannot be directly compared with other studies in which a greater proportion of patients had multivessel disease. In addition, stress echocardiography has the advantage of requiring only readily available equipment compared with that required for perfusion scintigraphy, and avoids the exposure to a radioisotope.

In this study we did not use the side-by-side analysis of rest- and stress-digitized image. However, it is unlikely that this could explain the relatively low sensitivity of the test, as we have recently reported³.

The increased sensitivity as a result of adding atropine was associated with only a small reduction in specificity; after dobutamine alone 31 of the 33 patients without coronary disease had a negative echocardiogram (specificity of 94%, 95%CI 80 to 99%) compared with 29 of 33 (specificity of 88%, 95%CI 72 to 97%) after the addition of atropine.

The effect of atropine in increasing diagnostic yield is also reflected by the changes in wall motion score index seen in group A. For patients with coronary artery disease in group A there was no significant increase in wall motion score index after dobutamine alone, but a significant increase after the addition of atropine. However in accordance with the lack of effect of atropine on specificity, wall motion score index did not increase after atropine in patients without coronary disease. Similarly in group B there

was an increase in wall motion score index at peak stress in patients with coronary disease, but no increase in those without coronary disease.

Safety of the combined stress test: There were no severe side effects at peak dobutamine or atropine and no difference between the incidence of side effects between groups A and B. In particular the requirement for metoprolol was the same between the 2 groups. This was usually given for chest pain that did not resolve within 5 minutes of stopping dobutamine. In those patients who developed ST elevation, metoprolol was immediately given and resulted in rapid resolution of ST elevation and chest pain in all cases. Although there were no severe arrhythmias (2 patients had 3 beats of ventricular tachycardia at peak stress, and 1 patient developed nodal rhythm with maintenance of normal blood pressure), the test should only be performed with attention to electrocardiographic monitoring, 12 lead ST-segment assessment and blood pressure recording, and with resuscitation facilities available.

Relationship to other studies: Recent studies of dobutamine echocardiography have reported sensitivities of 86 to 89% for detection of coronary disease^{16,17}. These sensitivities are outside the 95% confidence limits for sensitivity in our study but there are several important differences between these studies and ours. Cohen et al¹⁶ reported an overall sensitivity of 86% but their patients were studied without β blockade and 16 of 51 patients with significant coronary disease had 1-vessel disease, for whom the sensitivity was 69%, whereas sensitivity for patients with multivessel disease was 94% (33 of 35 patients). Sawada et al¹⁷ reported a sensitivity of 89%, but only a small amount of patients were taking β blockers and only patients with normal resting echocardiograms were considered in this analysis. Our overall sensitivity of 70% and the sensitivity of 93% for multivessel disease is comparable with the sensitivity of other imaging techniques including tomographic thallium imaging after exercise^{5,18} or pharmacological stress with adenosine⁵ or dipyridamole¹⁹.

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CHAPTER 4

DOBUTAMINE STRESS ECHOCARDIOGRAPHY BEFORE AND AFTER ANGIOPLASTY¹

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Abstract

Myocardial function was assessed by stress echocardiography in 28 patients before and after successful elective coronary angioplasty. Dobutamine stress echocardiography was performed using up to 40 $\mu\text{g/kg/minute}$, followed by addition of atropine in 20 patients to achieve 85% of the predicted maximal exercise heart rate. The initial studies were performed 1 day before and second ones within 3 days (mean 1.3) after angioplasty. The frequency of dobutamine-induced new wall motion abnormalities decreased from 20 (71%) before to 4 (14%) after angioplasty ($p < 0.0001$). Before angioplasty wall motion score index (an indicator of left ventricular wall motion, an increase in which index indicates impaired wall motion due to myocardial ischaemia) increased from 1.06 at rest to 1.23 at peak stress ($p < 10^{-6}$) but there was no significant increase in this index in the study after angioplasty. Before angioplasty, 14 (50%) patients developed chest pain during the stress test compared with 6 (21%) after angioplasty ($p = 0.05$), and before angioplasty the stress test was stopped before target heart rate was achieved, because of symptoms, ST-segment change or severe new wall

¹Am J Cardiol 1992;69:740-745

motion abnormality in 14 patients compared with 7 after angioplasty ($p = 0.09$). Thus early after angioplasty there is a reduction in myocardial ischaemia as assessed by dobutamine stress echocardiography.

Introduction

Non-invasive assessment of patients with suspected coronary artery disease is most often performed by exercise electrocardiography. However the limited sensitivity and specificity of this technique¹ have led to its combination with either radionuclide scintigraphy with planar² or tomographic imaging³ to identify stress induced perfusion defects, or with 2-dimensional echocardiography to identify abnormalities of left ventricular wall motion which develop with the onset of ischaemia^{1,4}.

An alternative is to combine echocardiography with non-exercise stress using atrial pacing⁵ or pharmacological stress using dobutamine⁶, dipyridamole⁷ or adenosine⁸. There is evidence from animal experiments that dobutamine, a sympathomimetic agent with both positive chronotropic and inotropic effects⁹, is the pharmacological stress agent of choice for combination with imaging techniques that assess left ventricular systolic function, including echocardiography¹⁰.

The stepwise incremental protocol in which the dose of dobutamine is increased and the increase in heart rate and blood pressure associated with dobutamine, make the test analagous to exercise stress testing⁶.

The effect of successful angioplasty has previously been assessed by exercise stress echocardiography¹¹ or perfusion scintigraphy¹² and by dipyridamole echocardiography¹³. However, we are not aware of data on the use of dobutamine stress echocardiography in this clinical setting. Accordingly, in this study we investigated if dobutamine stress echocardiography could assess the functional effect of the change in myocardial perfusion early after angioplasty.

Methods

Patient selection: Consecutive patients with stable angina pectoris in whom elective coronary angioplasty was planned were prospectively enrolled in the study. Previous infarction, angioplasty or coronary artery grafting were not contraindications. All patients gave informed verbal consent to undergo dobutamine stress echocardiography. It was considered unethical and potentially dangerous to withdraw antianginal

therapy including β -blockers, especially owing to the risk of rebound instability occurring at the time of angioplasty.

Dobutamine stress echocardiography: Patients underwent dobutamine stress echocardiography one day before, and within 3 days after elective angioplasty, unless there was some contraindication to repeating the study. Two-dimensional echocardiography was performed at rest using Hewlett-Packard Sonos 1000 echo apparatus with 2.5 and 3.5 Mhz transducers. Standard apical and parasternal views were recorded on video tape. The optimal transducer positions were marked on the chest and baseline 12-lead electrocardiograph recorded. When the standard position of a chest electrode coincided with the marked transducer position, the electrode was moved one space higher or lower.

Dobutamine was administered intravenously using an infusion pump, starting at a dose of 10 $\mu\text{g/kg/minute}$ for 3 minutes and increasing by 10 $\mu\text{g/kg/minute}$ every 3 minutes to a maximum of 40 $\mu\text{g/kg/min}$ (stage 4), which was continued for 6 minutes. Because antianginal therapy, including β blockers, was continued during the test, patients infrequently developed tachycardia despite exposure to high levels of dobutamine. Accordingly as was previously suggested¹⁴, 0.25 mg of atropine was given intravenously at the end of stage 4, and repeated up to a maximum of 1 mg with continuation of dobutamine to achieve 85% of the predicted maximum exercise heart rate in those patients who did not achieve this target heart rate and in whom the test was negative with dobutamine alone. In this way it was attempted to achieve the same peak heart rate in both stress tests before and after angioplasty.

Throughout the stress test, 2-dimensional echocardiogram was monitored; images were acquired by one of the authors and recorded on video tape for the last minute of each of stages 1 to 3, the last 4 minutes of stage 4 and continuously for up to 10 minutes after dobutamine was discontinued or after administration of atropine. Infusion was stopped if the patient developed an obvious new wall motion abnormality, ST depression > 2 mm 80 ms after the J point, ST elevation, significant chest pain, reduction in systolic blood pressure > 20 mm Hg from that at rest, or any side effect regarded as being due to dobutamine. Metoprolol was available and used to reverse the effects of dobutamine, if they did not revert spontaneously and quickly.

Angioplasty: was performed by the femoral route using standard equipment and techniques within 1 day of the initial stress echocardiography. Severity of the stenosis before and after the procedure was assessed by either visual or quantitative analysis¹⁵ without knowledge

of the results of the stress echocardiographic tests. Angioplasty was indicated in cases of persistent anginal symptoms despite medication, and of coronary disease with a diameter stenosis $\geq 50\%$. The result of angioplasty was considered positive if the diameter stenosis was reduced to $< 50\%$.

Echocardiographic assessment: In addition to assessment of echocardiographic images during acquisition, assessment was performed by 2 experienced investigators after acquisition. Both on-line and off-line assessments were performed without knowledge of the site of angioplasty or of patient's coronary anatomy before or after angioplasty. When there was disagreement between the 2 off-line assessors, a third investigator viewed the images without knowledge of the previous assessments and a majority decision was achieved. For this semiquantitative assessment, the left ventricular wall was divided into 16 segments¹⁶, and each segment was scored using a 4 point scale: 1 = normal, 2 = hypokinetic, 3 = akinetic and 4 = dyskinetic (Figure 1). The 16 segments were combined into 5 myocardial areas: anterior, septal, lateral, inferior and apical. The anterior, septal and lateral areas and septal, anterior and lateral segments of the apex were regarded as being in the territory of the left anterior descending coronary artery, whereas the inferior and lateral areas and apical inferior segment were in the territory of the circumflex or right coronary artery. An increase in score in ≥ 1 segment from rest to stress constituted a positive test. Using this scoring system, an index of global left ventricular wall motion (wall motion score index) was calculated as: the sum of scores in visualised segments/number of segments visualised, at baseline and peak stress for both studies before and after angioplasty.

Statistical analysis. Results are expressed as mean \pm standard deviation, and 95% confidence intervals are given where appropriate. Discrete variables were compared using the chi-square test and continuous variables using paired *t* tests.

Results

Study patients: Dobutamine stress echocardiography was performed in 48 consecutive patients in whom elective angioplasty was planned. Angioplasty was performed in 33 patients; the procedure was not performed in the remaining 15 because of $< 50\%$ diameter stenosis of the target vessel in 7 (stress echocardiogram negative in 6), multivessel disease not suitable for angioplasty in 4 (stress echocardiogram positive in 3), total occlusion of the target vessel in 3 (stress echocardiogram positive in 1) and

left main stem lesion in 1 (stress echocardiogram positive). Five patients undergoing angioplasty did not have stress echocardiography performed after angioplasty; 2 refused repeat study, 1 had acute infarction after angioplasty, 1 had tamponade at angioplasty and 1 had dissection and proceeded to bypass grafting. The data presented relate to the 28 patients who had dobutamine stress echocardiography before and after successful angioplasty.

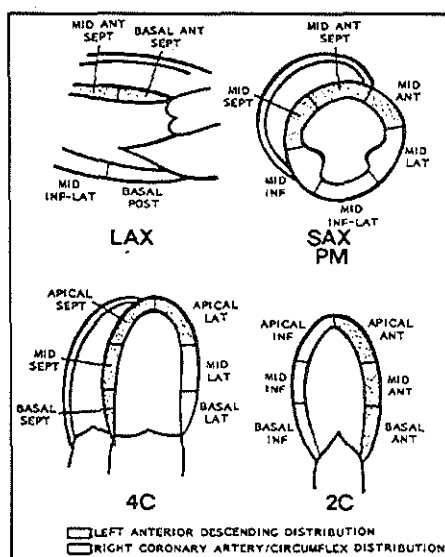


Figure 1. Representation of 16-segment regional wall motion analysis, derived from Bourdillon et al¹⁶. ANT = anterior; INF = inferior; LAT = lateral; LAX = parasternal long-axis view; POST = posterior; SAX PM = short axis at papillary muscle level; SEPT = septal; 2C = 2-chamber apical view; 4C = 4-chamber apical view.

Nineteen patients were men (mean age was 60 ± 11.6 years). Eleven patients had previous myocardial infarction, 4 had previous angioplasty and 2 had previous bypass grafting. Twenty-three patients were receiving β blockers, 14 oral nitrate preparations and 16 calcium antagonists.

Twenty-four patients had 1-vessel coronary disease. The target vessel was the left anterior descending in 11 cases, the right coronary artery in 11 and the circumflex in 7; 1 patient had lesions in 2 arteries dilated. For all 29 lesions the residual lesion after angioplasty was $<50\%$ diameter stenosis.

Stress echocardiography studies: All 28 patients underwent dobutamine stress echocardiography 1 day before and within 3 days after angioplasty. Mean time of the second study was 1.3 ± 0.6 days after angioplasty; in 22 patients, the study was repeated within 1 day after angioplasty.

Table I. Haemodynamic changes during stress testing before and after angioplasty.

	Base	Peak	p Value
Heart rate (beats/min)	Before PTCA 67 ± 12	121 ± 22	$<10^{-6}$
	After PTCA 73 ± 13	124 ± 24	$<10^{-6}$
	p value 0.03	0.59	
SP (mm Hg)	Before PTCA 133 ± 17	146 ± 22	0.002
	After PTCA 127 ± 17	138 ± 21	0.003
	p value 0.1	0.1	
Results expressed as mean \pm SD. PTCA = percutaneous transluminal coronary angioplasty, SP = systolic blood pressure.			

Table I shows the haemodynamic changes during the 2 studies. Atropine (up to 1 mg intravenously) was administered at the end of stage 4 to 20 patients, 15 in both studies before and after angioplasty, and 5 in one or the other study only. Twenty-three patients were receiving β blockers at the time of the study; 19 of the 20 who needed atropine were receiving β blockers. In both studies before and after angioplasty there was a significant increase in both heart rate and systolic blood pressure from base to peak stress. Although baseline heart rate was higher in the study after angioplasty, peak heart rate was the same in both studies. There was no significant difference between systolic blood pressure before and after angioplasty, at either baseline or peak stress.

Wall motion abnormalities at rest were seen in 5 patients on echocardiograms before and after angioplasty. Figure 2 shows the percentage of patients with stress induced new wall motion abnormalities, chest pain and ST segment changes before and after angioplasty. Before angioplasty, 20 (71%, 95% confidence interval 51 to 87%) developed new wall motion abnormalities compared with 4 (14%, 95% confidence interval 4 to 33%) after angioplasty ($p < 0.0001$). The frequency of positive stress echocardiography for each of the dilated coronary arteries is shown in table II.

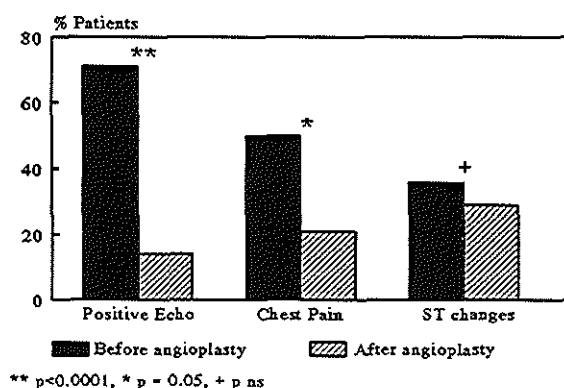


Figure 2. Percentage of patients with positive echo, chest pain and ST changes before and after angioplasty.

Table II Frequency of positive stress echocardiogram for each of the dilated coronary arteries.

Vessel Dilated	No. of Positive Echocardiograms (%)	
	Before PTCA	After PTCA
Left anterior descending	67 ± 12	121 ± 22
Left circumflex	73 ± 13	124 ± 24
Right coronary artery	0.03	0.59

PTCA = percutaneous transluminal coronary angioplasty.

Of the 20 patients with a positive test before angioplasty, the site of new wall motion abnormality was consistent with the diseased coronary artery in 17. In the remaining 3 patients, 1 with circumflex disease had new wall motion abnormality in the anterior and septal areas, 1 with right coronary disease had resting inferior abnormalities that extended to the posterior septum at stress, and the 1 who had lesions dilated in both left anterior descending and circumflex arteries developed changes in both inferior and lateral areas. The site of new wall motion abnormality was consistent with the site of the dilated vessel in 3 of the 4 patients with positive stress echocardiography after angioplasty; in the fourth (who had the 2-vessel

dilatation), the new wall motion abnormalities again developed in the inferior and lateral areas.

The frequency of chest pain also decreased; before angioplasty, 14 patients (50%, 95% confidence interval 31 to 69%) developed chest pain compared with 6 (21%, 95% confidence interval 8 to 41%) after angioplasty ($p = 0.05$). Before angioplasty, 10 patients (36%, 95% confidence interval 19 to 56%) developed ST changes (6 depression, 4 elevation), and 8 (29%, 95% confidence interval 13 to 49%) had ST changes after angioplasty (7 depression, 1 elevation).

The 85% of predicted maximal exercise heart rate for sex and age was achieved in 14 patients before angioplasty (1 for new wall motion abnormality, 5 for ST changes and 8 for chest pain) compared with 7 after angioplasty (1 for ST changes, 5 for chest pain and 1 for chills), $p = 0.09$.

Of the 4 patients with multivessel disease, the test after angioplasty was positive in 2, including the 1 who had 2 lesions dilated. Of the 2 patients with multivessel disease and a negative stress test after angioplasty, 1 had total occlusion of the right coronary artery, and 1 had previous coronary grafting with patent grafts. When patients with a previous myocardial infarct were separately analyzed, 10 of 11 had positive echocardiography before angioplasty compared with 2 after angioplasty. Furthermore, of 5 patients in this group, 4 had positive echocardiography before angioplasty, which was reduced to 2 after angioplasty.

To further assess the change in dobutamine-induced ischaemia before and after angioplasty, new wall motion abnormalities, chest pain and ST depression were regarded as markers of ischaemia, and the number of patients with 0, 1, 2 and 3 markers before and after angioplasty are shown in figure 3. The distribution of frequency of markers of ischaemia was different before and after angioplasty, with more patients having 2 or 3 markers before angioplasty, and more having no markers after angioplasty (chi-square 15.4, degrees of freedom 3, $p = 0.002$).

Wall motion score indexes: Regional wall motion analysis was performed in 95% of the ventricular segments, and a wall motion score was derived both before and after angioplasty. Before angioplasty, mean wall motion score index (figure 4) increased from 1.06 ± 0.15 at baseline to 1.23 ± 0.22 at peak stress ($p < 10^{-6}$). After angioplasty there was a small but insignificant increase in wall motion score index from 1.08 ± 0.20 to 1.10 ± 0.22 . There was no significant difference between baseline wall motion score indexes before and after angioplasty, but the index at peak stress was significantly higher in the study before angioplasty (1.23 ± 0.22 vs 1.10 ± 0.22 , $p = 0.00002$).

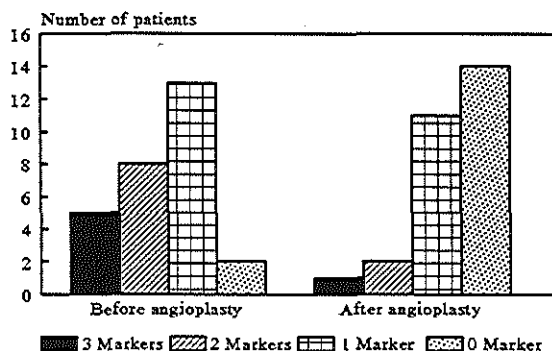


Figure 3. Number of patients with 3, 2, 1 and 0 markers of ischaemia during stress tests before and after angioplasty.

Complications: There were no serious complications related to either dobutamine or atropine. Before angioplasty, 2 patients had frequent ventricular ectopics including couplets, 1 had frequent atrial ectopics, 1 nodal rhythm and 1 chills. After angioplasty 1 patient had ventricular ectopics, 1 nodal rhythm and 1 chills. Metoprolol was needed by 10 patients before angioplasty either for relief of chest pain that did not resolve spontaneously within 5 minutes of stopping the stress test, or for ST elevation; after angioplasty, metoprolol was administered to 5 patients for the same reasons.

Discussion

This is the first study that uses dobutamine stress echocardiography for assessment of patients before and early after angioplasty. The reduction in frequency of development of new wall motion abnormalities, and difference in change in wall motion score index after angioplasty indicate the reduction in dobutamine-induced myocardial ischaemia after angioplasty. Similar changes were seen in the incidence of chest pain before and after angioplasty, although the use of such a subjective end point may be misleading, because patients may confuse discomfort associated with tachycardia with ischaemic heart pain, despite careful

questioning. The total incidence of ST segment changes (both elevation and depression) did not change after angioplasty; before angioplasty, 10 patients had ST changes, 4 of whom had elevation (2 with previous Q-wave infarction), and after angioplasty, 8 had ST changes, 1 of whom had ST elevation (no previous infarction). Of the latter 8 patients, the test after angioplasty was stopped for ST elevation in 1, chest pain in 2, and because an adequate heart rate was achieved in 5. Inspection of the data before angioplasty of these patients showed that the test was stopped for ST elevation in 2, pain in 5, and in only 1 did the test proceed to achievement of target heart rate. Therefore, although preliminary inspection of the data on ST segment changes suggests no reduction in ischaemia as assessed by ST changes, such inspection without consideration of other indicators of ischaemia may be misleading, because those patients with ST changes after angioplasty often stopped the stress test before angioplasty because of other evidence of ischaemia that may have occurred before ST changes. Accordingly, in an attempt to overcome such confounding influences of the various indicators of ischaemia, we used the number of patients completing the stress test (i.e. achieving 85% of the predicted maximal exercise heart rate, without significant chest pain or ST changes necessitating termination of the test). Although these results did not reach the conventional level of statistical significance, the trend was towards more patients completing the test after angioplasty (75% vs 50%; $p=0.09$).

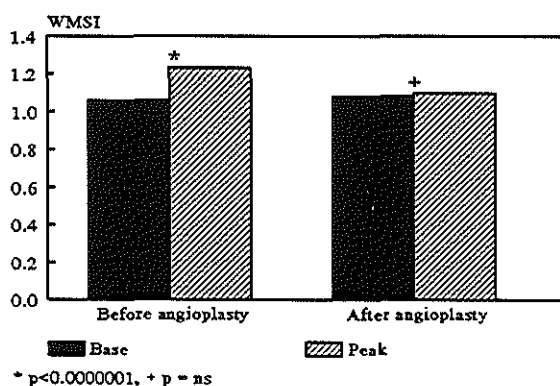


Figure 4. Mean wall motion score indices (WMSI) before and after angioplasty. ns = nonsignificant.

Similarly, a combination of ischaemic events during the test showed that more patients had no markers of ischaemia after angioplasty, and more had 2 or 3 markers of ischaemia before.

Twenty patients developed new wall motion abnormalities during the stress test before angioplasty, indicating a sensitivity of 71% for the detection of coronary artery disease. Recent data¹⁷ show that sensitivity of stress echocardiography for detection of coronary disease using dipyridamole is reduced in patients on antianginal therapy. Continuation of β blockers (as in 23 of these patients) antagonizes the β -adrenergic effect of dobutamine⁹, and this limited the sensitivity of dobutamine stress echocardiography in our laboratory⁶. Accordingly, the protocol for dobutamine stress echocardiography has been changed with the addition of atropine at the end of 15 minutes of dobutamine infusion (maximum dose 40 $\mu\text{g}/\text{kg}/\text{minute}$) in those patients who have not achieved 85% of the predicted maximal exercise heart rate and not developed obvious new wall motion abnormalities, ST changes, chest pain or side effects regarded as being due to dobutamine and needing termination of the test. Accordingly, 20 of these patients received atropine, 15 in both studies and 5 in either the study before or after angioplasty. Of 19 patients who received atropine in the study before angioplasty, off-line analysis showed a new wall motion abnormality that had been unrecognised during on-line assessment in 1 during dobutamine alone and in 11 after atropine. Using our previous protocol without the addition of atropine, dobutamine stress echocardiography would have been positive in 10 of 28 patients, resulting in a sensitivity of 36%.

The mean time to the stress test after angioplasty was 1.3 days; in 22 patients; the test was repeated within 1 day of angioplasty, and at this stage there was already a reduction in dobutamine-induced new wall motion abnormalities. The time of the study after angioplasty, and the frequency of patients with persisting positive studies are similar to those reported by Picano et al¹³ using dipyridamole as the stress agent. This is in contrast to a previous study reported by Manyari et al¹⁸ using exercise thallium scintigraphy to assess myocardial perfusion after angioplasty, which showed a delay in improvement in myocardial perfusion in 12 of 43 patients studied. Later repeat stress echocardiography may have detected a further improvement in myocardial function in our patients; however, our study is not directly comparable to that of Manyari, because thallium uptake is an indicator of perfusion and metabolic integrity¹⁹, whereas stress echocardiography, being dependent on the development of systolic dysfunction, is an indicator of true myocardial ischaemia.

In summary, this study shows that before angioplasty, stress echocardiography using dobutamine with the addition of atropine, if necessary, to achieve target heart rate has a sensitivity of 71% for detection of coronary artery disease in patients, with mainly 1-vessel disease on medication. The relief of a coronary stenosis reverses dobutamine stress-induced ischaemia early after angioplasty, and more patients proceed to complete the stress testing protocol without stopping because of chest pain, ST changes or obvious new wall motion abnormalities.

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CHAPTER 5

DOBUTAMINE STRESS-DOPPLER ECHOCARDIOGRAPHY BEFORE AND AFTER CORONARY ANGIOPLASTY¹

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Abstract

To determine if dobutamine-induced myocardial ischaemia causes abnormalities in Doppler parameters of left ventricular ejection and filling and to assess early effects of successful coronary angioplasty (PTCA) on these parameters, dobutamine stress echocardiography and Doppler studies were performed once in 11 normal volunteers and twice in 17 patients (within 1 day pre- and post-PTCA). Dobutamine induced wall motion abnormalities, ST changes and angina in 11, five and five patients, respectively, before and three, two and one patients, respectively, after PTCA. Doppler indices of both systolic and diastolic function were comparable at rest, before and after PTCA. Dobutamine induced similar increases in peak aortic velocity and average acceleration in healthy individuals (39% and 53%) and in patients with one-vessel disease both before (38% and 39%) and after PTCA (39% and 40%). In the three patients with multivessel disease peak aortic velocity showed a blunted response (-0.3%) before PTCA but increased by 17% after PTCA, while acceleration decreased both before (12%) and after PTCA (14%). There were significant differences ($p < 0.0001$)

¹European Heart Journal 1993;14:1011-1021

between healthy individuals and pre-PTCA patients in the effect of dobutamine on peak early (E) filling velocity (+34% vs -19%), E-acceleration (+35% vs -26%), peak early to atrial filling velocity ratio (E/A) (-0.7% vs -37%) and diastolic time velocity integral (TVI) (+34% vs -22%). After PTCA, the response of Doppler diastolic indices improved during dobutamine, as shown by the increase in E and E-acceleration (+8%, +24%, respectively) and by the decline in the reduction of E/A and TVI (-17% and -10%, respectively). Thus, the response of Doppler diastolic parameters to dobutamine stress is a sensitive indicator of significant coronary disease and is superior to changes in ejection indices. Successful PTCA resulted in improvement in diastolic filling response to dobutamine stress.

Introduction

Myocardial ischaemia causes changes in left ventricular systolic and diastolic function^{1,2}. Percutaneous transluminal coronary angioplasty (PTCA) is an effective therapeutic modality of revascularization for patients with significant coronary artery disease³. Improvements in left ventricular systolic and diastolic function either at rest or during stress have been reported after PTCA^{4,5}, but data concerning early improvements in resting left ventricular diastolic properties are conflicting^{5,6}. However, studies of left ventricular filling during exercise after PTCA have been limited to radionuclide angiography⁴. Doppler parameters of left ventricular ejection and filling have now been well validated⁷⁻⁹ and have been used to detect stress-induced myocardial ischaemia^{10,13,14}.

The use of pharmacological stress echocardiography with dobutamine for evaluating the functional significance of coronary disease is increasing^{15,16}. We have previously shown that dobutamine stress echocardiography is useful in detection of myocardial ischaemia and its reduction after PTCA^{16,17}. However no information is available concerning the effect of high dose dobutamine stress test on Doppler indices of left ventricular ejection and filling dynamics in patients undergoing PTCA.

The aims of this study were to determine whether dobutamine-induced myocardial ischaemia in patients undergoing PTCA causes abnormalities in Doppler-derived parameters of left ventricular systolic and diastolic function and to assess the early effect of successful PTCA on these parameters.

Subjects and Methods

Study population: This study included two groups. Group I consisted of clinically healthy volunteers (11 men, ranging in age from 25 to 67 years; mean 41) in whom the following criteria were satisfied: (1) no history of acute or chronic cardiac or any other disease, (2) normal physical examination, resting 12-lead electrocardiogram and two-dimensional echocardiogram with colour flow mapping and Doppler, (3) no use of any medication. Group II consisted of 20 consecutive patients with stable angina pectoris and >50% reduction in the luminal diameter of at least one major coronary artery referred for elective PTCA. Dobutamine stress test was not repeated after PTCA in three patients, one patient refused, and two patients had an PTCA-related complications. Group II, therefore, consisted of 17 patients (13 men and four women, ranging in age from 38 to 80 years; mean 60). No patient had left ventricular hypertrophy, frequent ectopy, valvular or congenital heart disease, significant valvular regurgitation (grade two or more) or impairment of the global left ventricular systolic function. Eight patients had prior myocardial infarction and two had previous PTCA. For ethical considerations and to avoid confounding effects of medications, the medical therapy was kept unchanged and at the same dosages both before and after PTCA. Twelve patients were treated with β blockers, eight with oral nitrates and seven with calcium antagonists. Fourteen patients had single-vessel disease and three had multivessel disease.

Dobutamine-stress test: All subjects gave informed verbal consent to undergo dobutamine stress test after full explanation of the procedure. Dobutamine stress test was performed once in the healthy individuals and twice in the patients (within 1 day pre- and post-PTCA). Following baseline 12-lead electrocardiography, blood pressure and two-dimensional echocardiography and Doppler, a graded dobutamine stress regimen of 10, 20, 30 and 40 $\mu\text{g/kg/min}$ in 3 min stages with the last stage (stage 4) lasting for 6 min, was started. Atropine (0.25 - 1 mg) was then added, while continuing dobutamine, if there were no signs of ischaemia including new wall motion abnormalities (WMA), ST changes or angina and 85% predicted maximum exercise heart rate was not achieved during dobutamine alone¹⁸. Twelve patients received atropine pre-PTCA and nine post-PTCA. Throughout the test, two-dimensional echocardiography and electrocardiography were continuously monitored, 12-lead electrocardiogram was recorded each minute and cuff blood pressure every 3 min. Criteria for discontinuation of the test were, ST

depression ≥ 2 mm 80 ms after the J point, ST elevation, significant angina or any complication regarded as being due to dobutamine.

Echocardiographic technique and analysis: Using a Hewlett-Packard Sonos 1000 echo apparatus, standard parasternal and apical views were acquired with 2.5 MHz transducer and recorded on VHS video-tape during the last minute of each of stages 1 to 3 and continuously for the last 4 min of stage 4 and during atropine. All echocardiograms were assessed on-line by the cardiologist and off-line by 2 experienced investigators without knowledge of the patient's clinical or angiographic data. Wall motion of the baseline and peak recordings were semiquantitatively assessed and scored using a 16-segment left ventricular model¹⁹ and a 4 point score: 1=normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic. An ischaemic response was defined as the development of new WMA associated with abnormal myocardial thickening in an area which was normal at rest or worsening of WMA at peak stress in a segment which was abnormal at rest. A wall motion score index was calculated as the sum of scores assigned to each segment divided by the number of segments and used as an index of global left ventricular wall motion.

Doppler technique and analysis: Doppler signals of ascending aortic blood flow and transmitral flow were recorded at baseline and peak dobutamine (stage 4) before addition of atropine. Aortic flow signals were obtained with the subject in the supine position by a 2.5 MHz nonimaging continuous wave Doppler transducer placed at the suprasternal notch. Using a 2.5 MHz pulsed Doppler transducer, the transmitral flow velocity profile was recorded from the apical four-chamber view while the patient was in the left lateral recumbent position, with the sample volume located at the mitral leaflet tips. Special care was taken to maintain the depth of the sample volume throughout each study both before and after PTCA. Doppler signals with simultaneous electrocardiogram and phonocardiogram were recorded on paper at a speed of 50-100 mm/s.

All Doppler measurements were performed by an experienced cardiologist by tracing the outermost portion of the velocity envelope utilizing an off-line computer, a digitizing tablet and a dedicated software program²⁰. Aortic peak velocity was measured and average acceleration was determined by dividing peak velocity by the time from onset of the flow to peak velocity. Parameters of left ventricular filling including peak velocities of both early (E) and atrial (A) diastolic filling and their ratio (E/A), peak E-wave acceleration and deceleration rates,

diastolic time velocity integral (TVI) and isovolumic relaxation period (time from aortic valve closure to the onset of mitral flow) with the corresponding heart rate were measured from simultaneous Doppler signals of mitral flow, phonocardiogram and electrocardiogram recordings. For each of the Doppler measurements eight consecutive cardiac cycles were analyzed and the results averaged.

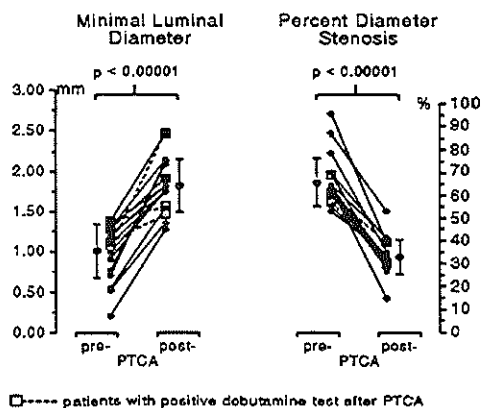


Figure 1 Individual, mean and standard deviation values of the minimal luminal diameter and percent diameter stenosis of the dilated coronary segment obtained by quantitative analysis before and after PTCA.

Coronary angioplasty: Using standard equipment and techniques²¹ angioplasty was performed within 1 day of the initial stress test. Quantitative analysis of the stenotic coronary segments pre- and post-PTCA was performed with the computer assisted Cardiovascular Angiography Analysis System (CAAS), which has been described and validated earlier^{22,23}. Standardization of acquisition and analysis of cineangiograms was done as previously described²⁴. The vessel dilated was the circumflex in nine, the left anterior descending in seven and the right coronary in two, including dilatation of two vessels in the only patient with two-vessel disease. PTCA was considered successful in all patients, defined as a $<50\%$ residual stenosis by visual inspection which has been confirmed quantitatively. The minimal luminal diameter of the dilated segment increased significantly from 1.01 ± 0.33 mm before to 1.82 ± 0.33 mm after PTCA (Figure 1). Also, there was a significant reduction in the % diameter stenosis from 62% before to 31% after

PTCA (Figure 1), which gives a mean difference in the stenosis diameter between pre- and post-PTCA of 31%.

Variability of measurements: Overall random variation (beat-to-beat variation plus intra-observer error) was estimated by applying a one-way analysis of variance to data from 14 randomly selected subjects, and expressed as standard deviation and percentage deviation (Table 1). Based on these results, the minimum significant difference needed to decide whether a change induced by dobutamine is indeed significant for an individual patient was defined as a percent change in Doppler parameter from baseline to peak dobutamine that exceeds the limits of the measurement variability.

Table 1. Measurement variability in Doppler transmitral flow parameters.

	Mean \pm SD	Random measurement variability	
		(SD)	(SD%)
E (cm/s)	66 \pm 19	3.6	\pm 5%
A (cm/s)	64 \pm 17	4.4	\pm 7%
E/A	1.2 \pm 0.5	0.116	\pm 10%
E-ACC (m/s ²)	9.4 \pm 2.9	1.12	\pm 12%
E-DEC (m/s ²)	3.8 \pm 1.1	0.334	\pm 9%
TVI (cm)	15.8 \pm 4	0.96	\pm 6%
IRP (ms)	78 \pm 14	3.059	\pm 4%
A = peak atrial filling velocity; E = peak early filling velocity, E/A = peak early to atrial filling velocity ratio; E-ACC = E-wave acceleration; E-DEC = E-wave deceleration; IRP = isovolumic relaxation period; SD = standard deviation; TVI = diastolic time velocity integral.			

Statistical analysis: Results are expressed as mean \pm standard deviation. Continuous variables, before and after dobutamine and before and after PTCA, were compared using paired t-test. The significance of the differences among the groups was assessed by an unpaired t-test. A level of $p < 0.05$ was considered to be statistically significant.

Results

Dobutamine-stress test: All patients had technically adequate echocardiograms and Doppler recordings. There were technical difficulties with the phonocardiogram in two patients and Doppler recordings of aortic flow in one patient.

Angina, ST changes and wall motion analysis: All subjects were in sinus rhythm. None of the healthy volunteers had dobutamine-induced markers of ischaemia. In all subjects hyperkinetic wall motion with enhanced systolic thickening were seen in the normal segments during dobutamine infusion. No serious complications occurred during the test.

Three patients with multivessel disease and prior myocardial infarction showed baseline WMA both before and after PTCA. These consisted of hypokinesia of the inferior wall in two patients and of the inferolateral wall in one patient. Wall motion score index was comparable before and after PTCA (1.05 ± 0.13 vs 1.07 ± 0.18 , $p=NS$).

Table 2. Markers of ischaemia during dobutamine stress test before and after PTCA.

Markers of ischaemia	pre-PTCA n = 17	post-PTCA n = 17
Wall motion abnormalities	11	3
ST changes	5	2
Angina	5	1
None	2	12

Table 3. Angiographic and echocardiographic findings in patients with post-PTCA dobutamine-induced WMA.

Cor.angio/DS%			WMA/SI	
			Base	Peak
1	Pre	CX/57% RC-LAD*	I/1.25	I/1.5
	Post	CX/37% RC-LAD*	I/1.25	I/1.5
2	Pre	LAD/65%		S/1.21
	Post	LAD/28%		S/1.21
3	Pre	CX/58% LAD/54%	I,L/1.5	I,L/2
	Post	CX/37% LAD/29%	I,L/1.75	I,L/1.88
* = total occlusion; Cor.angio/DS% = coronary angiography/percent diameter stenosis; CX = circumflex coronary artery; I = inferior; L = lateral; LAD = left anterior descending; pre and post = before and after PTCA; RC = right coronary artery; WMA/SI = wall motion abnormalities/score index.				

The frequency of dobutamine-induced markers of ischaemia before and after PTCA are shown in Table 2. Wall motion analysis before PTCA showed abnormalities that had been unrecognized during dobutamine alone in four patients after atropine, while after PTCA abnormalities occurred in one patient after atropine. Three patients had post-PTCA dobutamine-induced WMA which were the same as those pre-PTCA (Table 3). Wall motion score index increased significantly from 1.05 ± 0.13 to 1.24 ± 0.3 ($p = 0.003$) pre-PTCA, compared to insignificant increase from 1.07 ± 0.18 to 1.1 ± 0.22 ($p = 0.4$) post-PTCA. Both before and after PTCA the minimal luminal diameter and the % diameter stenosis did not differ between patients with and without dobutamine-induced WMA.

Table 4. Haemodynamic variables and Doppler parameters of left ventricular ejection and filling at baseline and peak dobutamine in healthy individuals and patients before and after PTCA.

	Healthy individuals		pre-PTCA		post-PTCA	
	Base	Peak	Base	Peak	Base	Peak
Haemodynamics						
HR (beats/min)	71±8	100±13*	63±9	108±18*	68±15	114±19*
SBP (mm Hg)	122±8	160±11*	131±14*	144±22*	121±11 ⁺	135±18*
Aortic indices						
PV (cm/s)	122±22	170±33*	117±31	155±49*	121±33	163±46*
A-ACC (m/s ²)	19±2	28.9±6*	16±1.4*	21±5.6*	17±1.6	22±6*
Mitral indices						
E (cm/s)	67±10	90±13*	62±13	50±13*	65±12	70±14* ⁺
A (cm/s)	50±10	67±12*	67±13*	85±13*	66±14	86±13*
E/A	1.4±0.4	1.4±0.4	0.9±0.3*	0.6±0.2*	1.1±0.3	0.8±0.2* ⁺
E-ACC (m/s ²)	10±1.5	13±2*	9.7±2	7±2.1*	11±3	13±2* ⁺
E-DEC (m/s ²)	4.3±0.8	5.1±1*	2.9±0.9*	3±0.7*	3.2±0.8	3.8±0.8* ⁺
TVI (cm)	13±2	17±1.7*	17±3*	13.2±2.7*	16.7±4	15±4*
IRP (ms)	78±4	55±6*	93±11	67±15*	92±12	65±9*

* $p < 0.01$ baseline vs dobutamine, # $p < 0.01$ Healthy individuals vs pre-PTCA, ⁺ $p < 0.01$ pre- vs post-PTCA. A = peak atrial filling velocity; A-ACC = average aortic acceleration; E = peak early filling velocity; E/A = peak early to atrial filling velocity ratio; E-Acc = E-wave acceleration; E-Dec = E-wave deceleration; HR = heart rate, IRP = isovolumic relaxation period; PV = peak aortic velocity; SBP = systolic blood pressure; TVI = diastolic time velocity integral.

Haemodynamic variables (Table 4): Heart rate and systolic blood pressure at peak dobutamine were not significantly different between the study groups. Addition of atropine at the end of stage 4, resulted in a significant increase in heart rate from 108 ± 18 to 128 ± 15 beats/min ($p < 0.001$) pre-PTCA and from 114 ± 19 to 130 ± 17 beats/min ($p < 0.001$) post-PTCA. In order to prevent a possible effect of a different heart rate on the Doppler response between the study groups, peak dobutamine in healthy volunteers was compared to peak dobutamine in patients before addition of atropine.

Doppler analysis: Because of the considerable overlap in the absolute Doppler values either at baseline or peak dobutamine between the study groups (Table 4, Figure 2 [a-c]), the % change from baseline to peak dobutamine was, in our hands, more reliable as an indicator of the Doppler response than the absolute values (Figure 3 [a-c]).

Doppler indices of left ventricular ejection (Table 4): As a group patients with coronary disease showed a significant increase in peak aortic velocity in response to dobutamine, which was comparable to the response in healthy volunteers. The increase in acceleration, however, was less in patients than in healthy individuals. There were no significant differences between pre- and post-PTCA values of both indices either at baseline or at peak dobutamine.

Subgroup analysis showed that the response of peak velocity and average acceleration was the same in healthy individuals (39% and 53%) and patients with single-vessel disease both before (38% and 39%) and after PTCA (39% and 40%). Patients with multivessel disease (the same patients with resting WMA) showed no significant differences in baseline values of both indices either before or after PTCA. However, these patients had a reduced acceleration both before (-12%) and after PTCA (-14%). Aortic velocity showed greater variability in response. Before PTCA, aortic velocity was reduced in two patients (one with total occlusion of two major coronaries in addition to the dilated artery and the other with <50% stenosis of two major arteries in addition to the target artery), but increased in the only patient with >50% stenosis of two vessels. After PTCA the aortic velocity response was modified to an increase of 17% compared to the blunted response (-0.3%) before PTCA.

No significant differences existed in the response of both indices between patients with and without dobutamine-induced WMA before PTCA. However, after PTCA patients with dobutamine-induced WMA showed reduction in acceleration (-18%) which did not differ from

before PTCA (-8%). Similarly the aortic velocity response in these patients remained blunted (8%) after PTCA compared to before PTCA (6%).

No significant differences existed in either baseline or the % change of both indices between patients with and without myocardial infarction before or after PTCA.

Doppler indices of left ventricular filling: At baseline, patients had a higher A, but a lower E/A ratio and E-wave deceleration, longer isovolumic relaxation period and larger TVI compared to healthy individuals (Table 4). Baseline values of filling indices did not differ before and after PTCA (Table 4), or among patients with and without myocardial infarction or in those with and without resting or dobutamine-induced WMA either before or after PTCA.

Three patterns of response of Doppler indices of left ventricular filling to dobutamine were defined, based on random measurement variability. The first response was a significant increase from baseline to peak dobutamine. The second was a blunted or insignificant change. The third was a significant decrease from baseline to peak dobutamine.

Changes in A, E-deceleration and isovolumic relaxation period with dobutamine did not differ among all groups (Table 4). The mean % change of E/A showed a flattened response in healthy individuals, a significant fall in patients before PTCA and a significant reduction in fall post-PTCA compared to pre-PTCA (Table 4). However there was overlap in the % change of this parameter between the three groups (range of -21% to 20% in normals, -16% to -56% pre-PTCA, and -36% to 7% post-PTCA).

The Doppler indices that showed pronounced difference in their response to dobutamine between the study groups were E, E-acceleration and TVI. There was no overlap in the % change of these indices between healthy volunteers and pre-PTCA patients (Figure 3 [a-c]). All healthy individuals had a significant increase in the three indices except one subject had a blunted response of E-acceleration (Table 5). Both before and after PTCA the patients had two types of response of these indices to dobutamine. Prior to PTCA the response was a significant decrease (majority) or blunted response (minority). Post-PTCA the response of E and E-acceleration changed to a significant increase in 13 patients and a blunted response in four, while the response of TVI was heterogenous, as shown in Table 5.

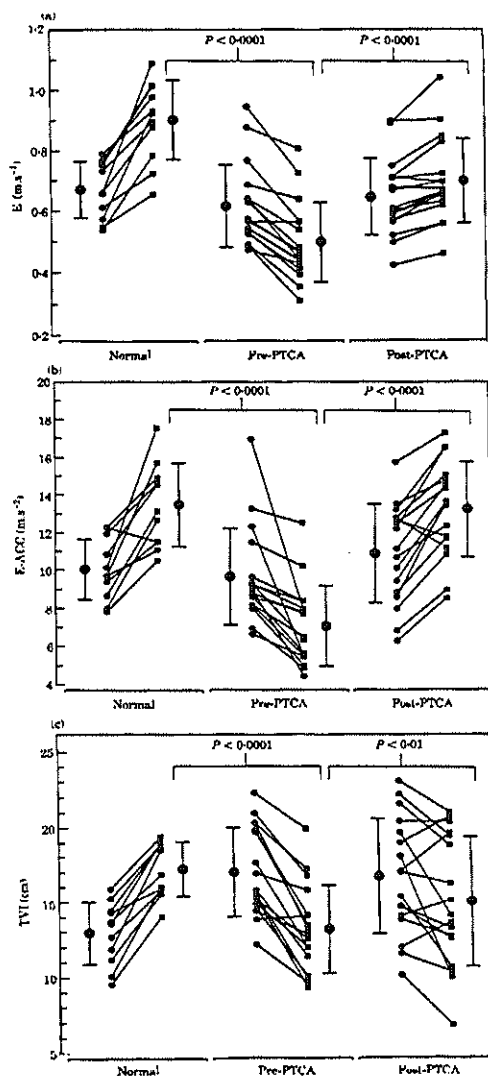


Figure 2 Individual, mean and standard deviation values obtained at baseline and peak dobutamine from healthy individuals and patients before and after PTCA. (a) peak early (E) filling velocity; (b) E-wave acceleration (E-ACC); (c) diastolic time velocity integral (TVI).

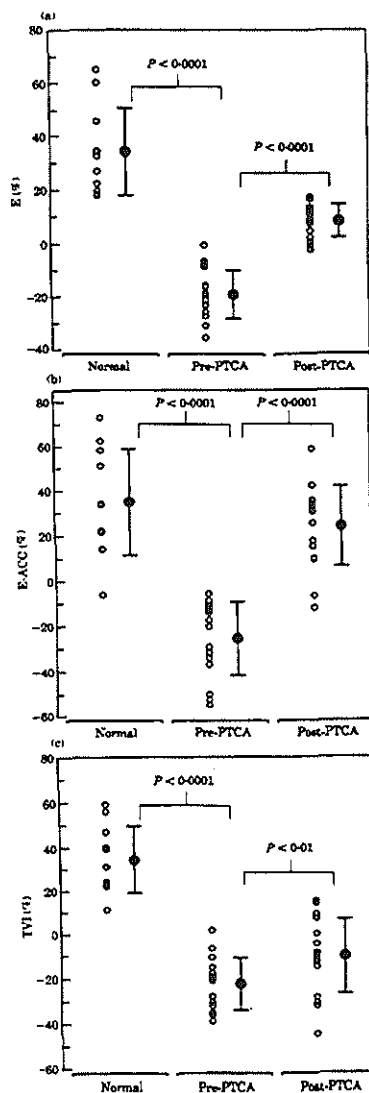


Figure 3 Individual, mean and standard deviation values of the % change from baseline and peak dobutamine, in healthy individuals and patients before and after PTCA. The levels that distinguished between the three groups are (a) peak early (E) filling velocity; (b) E-wave acceleration (E-ACC); (c) diastolic time velocity integral (TVI).

Before PTCA, there was a greater reduction in E among patients with, compared to those without, dobutamine-induced WMA, including patients with previous myocardial infarction and those with multivessel disease or baseline WMA, (-23% vs -13%, $p < 0.01$). However, no significant difference existed in the response of filling indices between these subgroups after PTCA.

Table 5. Classification of dobutamine-induced responses in Doppler indices of flow in relation to clinical status.

Healthy individuals (n=11)			pre-PTCA (n=17)		post-PTCA (n=17)	
	n	Mean %, range	n	Mean%, range	n	Mean%, range
E		34%		-19%		8%
↑	11	18 to 65			13	5 to 17
--			1	-0.5	14	-2 to 2
↓			16	-7 to -36		
E-ACC		35%		-26%		24%
↑	10	14 to 72			13	15 to 59
--	1	-6	4	-7 to -11	4	-11 to 10
↓			13	-12 to -36		
TVI		34%		-22%		-10%
↑	11	11 to 59			4	7 to 15
--			1	2	2	0.1 to -4
↓			16	-7 to -39	11	-8 to -44

(↑) = significant increase, (--) = blunted response, (↓) = significant decrease; E = peak early filling velocity; E-Acc = E-wave acceleration rate; Mean % and range = mean and range of the percent change from base to peak dobutamine, n = number of subjects; TVI = diastolic time velocity integral.

Discussion

This study addresses the response of Doppler derived parameters of left ventricular systolic and diastolic performance to high dose dobutamine stress testing in the evaluation of patients with significant coronary disease before and after PTCA.

Dobutamine stress test: We confirm the recently reported usefulness of dobutamine stress echocardiography in the diagnosis of coronary artery disease (CAD)¹⁶ as well as its value in the detection of reduction in stress-induced myocardial ischaemia early after PTCA¹⁷. The sensitivity of stress echocardiography for detection of CAD in our patients (mainly

single-vessel disease and on medication) is 65% which is higher than that of chest pain (29%) or ST changes (29%). The relatively low sensitivity of dobutamine-echocardiography for diagnosis of coronary disease in this study could be related to the small number of patients with multivessel disease (3/17), which increases the number of positive tests¹⁶ and to the possible effect of medications.

Improvements in stress-induced ischaemia occurred after PTCA, as evident by the increased frequency of patients lacking markers of ischaemia (12 patients after PTCA vs two before PTCA). The time of the post-PTCA study and the frequency of patients with persistent stress-induced WMA are similar to those reported by Picano et al²⁵ using dipyridamole as the stress agent. Although the finding of persistent WMA after PTCA can be explained by incomplete revascularization, as was present in one patient, other mechanisms such as PTCA-induced local trauma and distal vasoconstriction or embolization, are possible²⁶.

Doppler indices of left ventricular ejection: Peak aortic velocity and aortic acceleration have been shown to be altered by the presence of significant coronary disease in response to exercise or dipyridamole stress^{27,28}. In this study the absolute baseline and peak dobutamine values of peak velocity did not differ among all groups, while those of average acceleration were lower in patients than in healthy individuals. However, both indices were comparable before and after PTCA. The differences in the absolute values of acceleration can be attributed to the effect of aging³⁰, medication³¹ and the possible technical problems in conditions such as horizontal hearts or atherosclerotic aorta.

The insignificant difference in the response of both peak velocity and acceleration seen before and after PTCA and between patients with single-vessel disease and healthy individuals or those with and without dobutamine-induced WMA suggest that the extent of dobutamine-induced ischaemic myocardium was not large. Compensatory-enhanced contractility in normal segments may have masked the presence of regional dysfunction. In contrast, the blunted response of peak velocity and the reduction in acceleration in patients with multivessel disease suggest that the extent of stress-induced ischaemic myocardium may have been larger, with the normal segments unable to compensate in order to enhance the global left ventricular performance in the presence of advanced coronary disease. Despite differences in methodology, this finding is supported by those of Bryg et al²⁷ and Labovitz et al²⁸ who showed that the response of aortic peak velocity and acceleration to exercise and dipyridamole stress were particularly sensitive in the

detection of multivessel disease. Our findings are in agreement with those of Mazeika et al²⁹ who studied the effect of dobutamine (up to 20 $\mu\text{g/kg/min}$) on pulsed-Doppler left ventricular ejection indices and observed similar response in healthy individuals and coronary patients and a blunted response in six patients with WMA in ≥ 3 segments all of whom had multivessel disease.

Doppler indices of left ventricular filling: The Doppler pattern of left ventricular filling obtained in our patients at baseline demonstrated greater contribution of atrial filling, slower deceleration rate of early filling and a longer isovolumic relaxation period as compared to healthy individuals. This pattern is consistent with previous Doppler reports^{6,32} of diastolic filling abnormalities in patients with coronary artery disease. However, the interpretation of this pattern as an indicator of coronary artery disease may be difficult due to the possible effect of anti-anginal medications, the overlap of the individual values between groups (Figure 2 [a-c]) and finally the nonspecificity of this pattern for coronary disease³³. On the other hand, changes in baseline values of Doppler indices after PTCA were insignificant. This finding is consistent with previous Doppler and radionuclide reports of unchanged resting diastolic parameters early after PTCA^{4,6}. In contrast, there is disagreement between our findings and those of Castello et al⁵ who showed modification in left ventricular filling pattern in 31 patients (16 with unstable angina) 24 hours after PTCA, and those of Masuyama et al³⁴ who demonstrated gradual improvement in diastolic filling in 50 patients (25 with multivessel disease) 2 and 9 days after PTCA. Differences in patient populations and methodology may explain these findings.

Changes in E, E-acceleration, E/A and TVI induced by dobutamine were the most useful for distinguishing healthy subjects from pre-PTCA patients and for identifying the beneficial effects of PTCA (Figure 3 [a-c]). In healthy subjects E, E-Acc and TVI increased significantly while E/A remained unchanged. In contrast, the response of these parameters in pre-PTCA patients was different and significantly decreased. After PTCA, improvements in the response of these indices occurred during dobutamine, as evidenced by changing the direction of the response for E and E-acceleration from decreasing pre-PTCA to increasing post-PTCA and by the significant decline in the reduction of E/A and TVI post-PTCA compared to pre-PTCA. If one consider that a significant increase (above the limits of measurement variability) is the normal response of Doppler filling indices to dobutamine, and a significant decrease (below the limits of measurement variability) and/or a blunted

response (within the limits of measurement variability) is the abnormal responses (Table 5), the response of E to dobutamine: (1) correctly identified 11 of 11 healthy individuals, (2) predicted the presence of significant coronary disease in 17 of 17 patients, and (3) identified improvements after PTCA in 13 of 17 patients (Table 5). Although E failed to increase in four patients after PTCA, there was a significant modification among those four in whom the response changed from a significant decrease of -21% pre-PTCA to a blunted response of -0.8% post-PTCA (Figure 2 [a]).

The pattern of augmented diastolic filling seen in healthy subjects is in agreement with previous clinical^{35,36} reports, which demonstrated that inotropic stimulation utilizing dobutamine increases early filling rate with augmented filling velocities. The response of Doppler indices of diastolic filling to dobutamine in our patients was similar to that previously reported in patients during ischaemia induced by coronary occlusion during PTCA², pacing¹³ or dipyridamole stress¹⁴. Despite the absence of simultaneous intracardiac pressure and quantitative left ventricular volume measurements, these abnormalities in the response of mitral velocity pattern to high dose dobutamine suggest that dobutamine induced myocardial ischaemia was a possible mechanism for these alterations. This is further supported by the observed greater reduction in E in patients with, as compared to patients without, new WMA at peak dobutamine.

Our observation of improved Doppler response of diastolic function during dobutamine after PTCA is in agreement with that of Lewis et al⁴, who demonstrated improvement in exercise diastolic function after PTCA as assessed by radionuclide angiography. The inability of Doppler filling indices to respond to dobutamine after PTCA to the same extent as in healthy individuals may be explained by the differences in age between the two groups or by the concept of stunned myocardium³². Repeated later, the test could have shown further normalization of the Doppler response.

Limitations of the study: Doppler patterns of left ventricular ejection and filling are influenced by a number of well known factors^{25,27,28}. Some of these are particularly relevant to this study. A number of our patients had received anti-anginal medications, including β -blockers, which may have attenuated the effect of dobutamine to induce myocardial ischaemia^{16,26}. However, since medications were not changed during studies, we believe that this should not affect our results. A second problem is the age differences between healthy individuals and coronary

patients which, may explain some of the observed abnormalities in the response of Doppler diastolic indices before PTCA. However, the fact that the Doppler response of filling indices changed towards the normal after PTCA suggests that the abnormalities seen before PTCA were the results of coronary disease rather than aging alone. Finally, other factors which may confound analysis of Doppler profile, such as significant arrhythmias and fusion of E and A waves at high heart rates were not a problem in our population.

Conclusions. The response of Doppler parameters of left ventricular filling during dobutamine stress testing is a more sensitive indicator of significant coronary disease than that of ejection parameters. Dobutamine-induced changes in Doppler indices of left ventricular ejection were the same before and after PTCA. The evaluation of the response of left ventricular filling to dobutamine stress before and early after successful PTCA in the same patient was useful in identifying improvements in diastolic response that were not evident at rest. These initial results suggest that Doppler examination of mitral flow could be usefully added to wall motion analysis during dobutamine stress test.

Acknowledgment

We like to acknowledge the team of the catheterization laboratory of the Thoraxcenter for the advice and support for the quantitative assessment of coronary angiograms.

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CHAPTER 6

ABNORMAL LEFT VENTRICULAR EARLY DIASTOLIC FILLING DURING DOBUTAMINE STRESS DOPPLER ECHOCARDIOGRAPHY IS A SENSITIVE INDICATOR OF SIGNIFICANT CORONARY ARTERY DISEASE¹

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Abstract

Objective. This study was designed to assess changes in Doppler parameters of left ventricular ejection and filling in response to high dose (40 $\mu\text{g/kg/min}$) dobutamine stress and their utility in detection of coronary artery disease compared to new wall motion abnormalities.

Methods. Ten patients with low likelihood of coronary artery disease, served as a control group, and 23 patients with documented single vessel coronary artery disease underwent baseline and peak dobutamine - echocardiography and Doppler studies.

Results. In both groups dobutamine induced similar increases in heart rate and systolic blood pressure. During the test 14 patients had new wall motion abnormalities, 13 angina, and 7 ST changes. No markers of ischemia occurred in the control subjects. Dobutamine induced

¹J Am Coll Cardiol 1994; in press

qualitatively similar changes from baseline to peak in controls and patients in peak aortic velocity (46% vs 42%, $p=NS$), average aortic acceleration (61% vs 43%, $p=0.04$), and systolic time velocity integral (7% vs 2%, $p=NS$). Dobutamine caused marked increases in controls and decreases in patients in peak early filling velocity (E) (33% vs -22%, $p<0.0001$), and average E-acceleration (76% vs -28%, $p<0.0001$). The response of Doppler early filling indices to dobutamine stress was abnormal in all patients. There was no overlap in the percent change from baseline to peak dobutamine, between controls and patients for E and E-acceleration.

Conclusions. During dobutamine-stress test, an abnormal response of Doppler parameters of left ventricular early filling is a more sensitive marker of significant single vessel coronary disease than new wall motion abnormalities and is far superior as a predictor of coronary artery disease than the response of Doppler ejection parameters.

Introduction

Myocardial ischemia is well known to alter both systolic and diastolic properties of the left ventricle^{1,2}. Both peak velocity and acceleration of blood out of the left ventricle are closely correlated with global left ventricular performance^{3,4}, and have been used to detect stress induced ischemia in man^(5,6). It has been proposed that left ventricular diastolic function can be more susceptible to ischemic disturbance than systolic function, in addition, changes in diastolic parameters often precede systolic changes and therefore may be more sensitive indicators of myocardial ischemia^{2,7,8}. Doppler echocardiography is a noninvasive technique that is capable of providing beat to beat information about left ventricular ejection^{3,4} and filling dynamics⁹ either at rest or during stress.

We have previously shown that dobutamine stress echocardiography is useful in detection of myocardial ischemia^{10,11}. However, no information is available regarding the changes in Doppler parameters of either left ventricular ejection or filling in response to high dose dobutamine in subjects with and without coronary artery disease (CAD). This study was undertaken to assess the changes in Doppler-derived parameters of left ventricular systolic and diastolic function induced by high dose dobutamine-stress and their utility in detection of CAD compared to wall motion analysis.

Methods

Study population: This study comprised two groups. Group I consisted of 10 patients (6 men and 4 women with a mean age of 51 ± 9 years) referred for stress perfusion scintigraphy for assessment of atypical chest pain and low likelihood of CAD. They fulfilled the following criteria: (1) no history of cardiovascular disease, (2) normal physical examination, resting 12-lead electrocardiogram (ECG) and two-dimensional echocardiogram with colour flow mapping and Doppler, (3) normal symptom limited exercise ECG and perfusion technetium-99m MIBI single photon emission computed tomography. This population served as a control group.

Group II consisted of 23 patients (19 men and 4 women, with a mean age of 56 ± 11 years) with stable angina pectoris and $\geq 50\%$ diameter stenosis in a single major coronary artery and in whom elective angioplasty was planned. Patients with left ventricular hypertrophy, frequent ectopy, valvular or congenital heart disease, significant valvular regurgitation (grade two or more) or impairment of global left ventricular systolic function (ejection fraction < 0.50) were excluded. Ten patients had history of old myocardial infarction. Antianginal medication could not be discontinued in our patients. Fifteen patients were treated with beta blockers, 13 with nitrates and 10 with calcium antagonists.

Study protocol: All subjects gave informed verbal consent to undergo dobutamine stress test after full explanation of the procedure. Following recordings of baseline ECG, blood pressure and two-dimensional echocardiography including Doppler, a graded dobutamine infusion was started at and increased by $10 \mu\text{g/kg/minute}$ at 3 minutes stages to a maximum of $40 \mu\text{g/kg/min}$ with the last stage for 6 minutes. Atropine ($0.25 - 1 \text{ mg}$) was added while continuing dobutamine in patients without signs of ischemia (wall motion abnormalities, ST-changes, angina) who had not achieved 85% predicted maximum exercise heart rate during dobutamine alone¹². Two-dimensional echocardiography and ECG were continuously monitored. ECG was recorded each minute and cuff blood pressure every 3 minutes. Criteria to stop the test were, ST depression $\geq 2 \text{ mm}$ 80 ms after the J point, ST elevation, significant angina, significant arrhythmia or any complication regarded as being due to dobutamine.

Echocardiographic technique and analysis: Standard parasternal and apical views were acquired using a Hewlett-Packard Sonos 1000 echo

apparatus with 2.5 MHz transducer. The optimal transducer positions were marked on the chest. Echocardiograms were recorded on VHS video-tape during the last minute of each of stages 1 to 3, and continuously for the last 4 minutes of stage 4 and continuously for up to 10 minutes after discontinuation of infusion.

Wall motion analysis: Without knowledge of the patient's clinical or angiographic data, all echocardiograms were assessed on-line by the cardiologist and off-line by 2 experienced investigators. Wall motion and thickening of the baseline and peak recordings were semiquantitatively assessed and scored using a 16-segment left ventricular model¹³ and a 4 point score: 1=normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic. The development of new wall motion abnormalities associated with worsening of wall thickening constituted a positive test. We did not use a continuous loop format because we have previously tested whether cine loop analysis of dobutamine echocardiography had advantages for the interpretation of the images over the analysis from video tape and found the same results by the two techniques¹².

Doppler technique: Doppler signals of the ascending aortic blood flow and the transmitral flow were obtained at baseline and peak dobutamine. With the subject in supine position, the ascending aortic blood flow velocity was obtained with 2.5 MHz non-imaging continuous wave Doppler transducer placed at the suprasternal notch. The transducer was positioned to gain optimal signals as judged by a combination of acoustic and visual feedback. Using the apical 4-chamber view in the left lateral recumbent position, the transmitral blood flow velocity profile was recorded using a 2.5 MHz pulsed Doppler imaging transducer, with the sample volume located at the mitral leaflet tips. To maintain the sample volume location at the mitral leaflet tips the depth of the interrogation was recorded at baseline and reproduced at peak dobutamine. Doppler signals with simultaneous ECG and phonocardiogram were recorded on paper at a speed of 50-100 mm/s.

Analysis of Doppler data: All Doppler studies were analyzed by an experienced cardiologist by tracing the maximum velocity envelope. All measurements were performed utilizing an off-line computer, a digitizing tablet and a dedicated software. The following Doppler-derived parameters of left ventricular filling were measured: peak early filling velocity (E), peak atrial filling velocity (A), peak early to atrial velocity ratio (E/A), average E-wave acceleration rate (determined by dividing peak E by the time from onset of the flow to peak E), average E-wave deceleration rate (determined by dividing peak E by the time from onset

of the flow to an extrapolation of the deceleration slope to the baseline), total diastolic time-velocity integral (TVI_D), corresponding heart rate and isovolumic relaxation period (time from aortic valve closure on the phonocardiogram to the onset of mitral flow). Similarly, peak aortic velocity and total systolic time-velocity integral (TVI_S) were measured from the Doppler signals of aortic flow and average acceleration was determined by dividing peak velocity by the time from onset of the flow to peak velocity. For each of the Doppler measurements eight consecutive cardiac cycles were analyzed and the results averaged.

Coronary angiography: Angiography was performed within one day from dobutamine stress test with the use of standard techniques, with visualization of the coronary arteries in multiple projections. Quantitative analysis of the stenotic coronary segments was performed with the computer assisted Cardiovascular Angiography Analysis System (CAAS), which has been described and validated earlier¹⁴. Standardization of acquisition and analysis of cineangiograms was done as previously described¹⁵. The stenosed vessel was the left anterior descending in 11 patients, the circumflex in 8 and the right coronary in 4. Quantitative analysis was not performed in 2 patients because of total occlusion of the left anterior descending in one patient and the right coronary in another. The median % diameter stenosis was 62% (range 50% - 100%).

Statistical analysis: Data are expressed as mean \pm standard deviation. We used an unpaired *t*-test to compare between control subjects and patients and the paired *t*-test to compare between baseline and peak dobutamine. A level of $p < 0.05$ was considered to be statistically significant.

Results

Dobutamine-stress test: All patients had technically adequate echocardiograms and Doppler recordings of the mitral flow. There were technical difficulties in the phonocardiographic detection of the aortic component of the second heart sound in two patients. There were difficulties in the recordings of the aortic flow in 6 patients, therefore, data from Doppler aortic flow relate to 17 patients.

Angina, ST changes and wall motion analysis: All subjects were in sinus rhythm. None of the patients in group I developed angina, ST changes or wall motion abnormalities. In this group dobutamine infusion induced hyperkinetic wall motion with enhanced systolic thickening.

Resting wall motion abnormalities were detected in 3 patients. In the group of patients with CAD during peak stress, including addition of atropine, new wall motion abnormalities occurred in 14 patients, angina in 13 and ST changes in 7 (6 depression > 1 mm and 1 elevation). Of the 18 patients who received atropine, wall motion analysis showed new wall motion abnormalities that had been unrecognized during dobutamine alone in 7 patients after atropine. New wall motion abnormalities occurred in 8/11 patients with left anterior descending disease and in 6/12 with left circumflex or right coronary artery disease. No serious complications occurred during the test.

Hemodynamic variables (Table 1): At baseline heart rate was significantly lower in patients compared to controls, however, there were no differences in the hemodynamic variables between the two groups at peak dobutamine. In order to prevent a significant effect of heart rate on the Doppler response between the study groups and to avoid problems such as fusion of E and A waves at high heart rate, peak dobutamine in the control subjects was compared to peak dobutamine in patients with CAD before addition of atropine.

Doppler aortic flow variables : Table 1 shows the mean \pm standard deviation values, at baseline and peak dobutamine, of aortic flow indices in control subjects and CAD patients. There were no significant difference in baseline values of aortic flow indices between control subjects and patients. Dobutamine resulted in a significant increase in peak aortic velocity in control subjects and patients (46% vs 42%, respectively, $p = 0.6$). Average aortic acceleration increased significantly with dobutamine in both groups, however, the increase in the control subjects was significantly higher than in patients (61% vs 43%, respectively, $p = 0.04$). The systolic time velocity integral increased slightly in the control subjects and patients (7% vs 2%, $p = 0.4$). Comparison between patients with and without new wall motion abnormalities at peak stress showed no significant difference in any of the aortic flow indices between the two subgroups.

Doppler transmitral flow variables: The mean \pm standard deviation values of Doppler transmitral variables at baseline and peak dobutamine in the study groups are also presented in Table 1.

At baseline, patients had lower E-deceleration, longer isovolumic relaxation period and larger TVI_D as compared to controls (Table 1). There were pronounced differences, between control subjects and CAD patients, in the effect of dobutamine on Doppler indices of left ventricular filling. In control subjects dobutamine induced marked and

significant increases in E, A, E-acceleration and TVI_D (Figures 1 and 2), marked shortening in isovolumic relaxation period and no change in E/A ratio or E-deceleration (Table 1). In patients, changes in response to dobutamine showed significant reduction in E, E-acceleration, TVI_D (Figures 1 and 2), E/A ratio and isovolumic relaxation period, with a significant increase in A (Figure 1).

Table 1: Hemodynamic variables and Doppler parameters of left ventricular systolic and diastolic function at baseline and peak dobutamine in control subjects and patients with CAD.

	Control subjects		Patients with CAD	
	Base	Peak	Base	Peak
Hemodynamic variables				
HR (bpm)	74 ± 8	112 ± 14*	62 ± 8 [#]	109 ± 16*
SBP (mm Hg)	131 ± 7	160 ± 14*	133 ± 14	153 ± 24*
DBP (mm Hg)	78 ± 6	81 ± 8	78 ± 7	85 ± 8
Aortic flow indices				
PV (cm/s)	105 ± 16	154 ± 30*	120 ± 29	168 ± 41*
A-Acc (m/s ²)	17.1 ± 1.5	27.4 ± 4.6*	16 ± 1.6	22.4 ± 4.9* [#]
TVI_S (cm)	20 ± 4.3	21.5 ± 5.2*	25.3 ± 7.7	25.7 ± 8.3
Mitral flow indices				
E (cm/s)	65 ± 9	85 ± 13*	69 ± 13	54 ± 9* [#]
A (cm/s)	57 ± 11	79 ± 19*	66 ± 13	86 ± 13*
E/A	1.2 ± 0.2	1.1 ± 0.3	1.1 ± 0.3	0.6 ± 0.1* [#]
E-Acc (m/s ²)	9.8 ± 1.3	17.3 ± 3.4*	10.8 ± 2.4	7.7 ± 2.1* [#]
E-Dec (m/s ²)	4.2 ± 0.9	4.6 ± 1	3.3 ± 0.9 [#]	3.2 ± 0.6 [#]
TVI_D (cm)	13 ± 2	15.4 ± 1.4*	18.3 ± 2.8 [#]	13.6 ± 2.5* [#]
IRP (ms)	81 ± 6	58 ± 7*	92 ± 10*	68 ± 14.
* p < 0.01 baseline vs dobutamine, # p < 0.05 control subjects vs patients with CAD. A = peak atrial filling velocity, A-Acc = average aortic acceleration, DBP = diastolic blood pressure, E = peak early filling velocity, E/A = peak early to atrial filling velocity ratio, E-Acc = E-wave acceleration, E-Dec = E-wave deceleration, HR = heart rate, IRP = isovolumic relaxation period, PV = peak aortic velocity, SBP = systolic blood pressure, TVI_D and TVI_S = diastolic and systolic time velocity integral, respectively.				

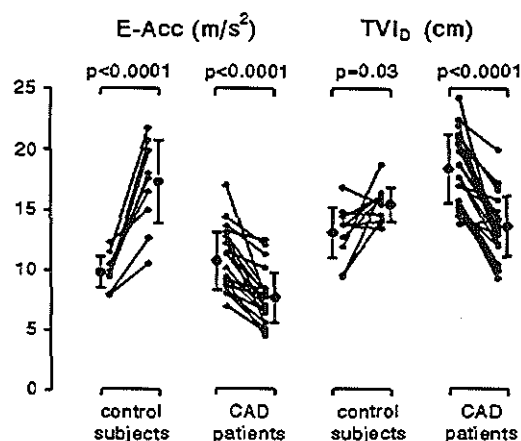


Figure 1: Individual, mean and standard deviation values of peak early (E) and atrial (A) filling velocities obtained at baseline and peak dobutamine from control subjects and patients with CAD.

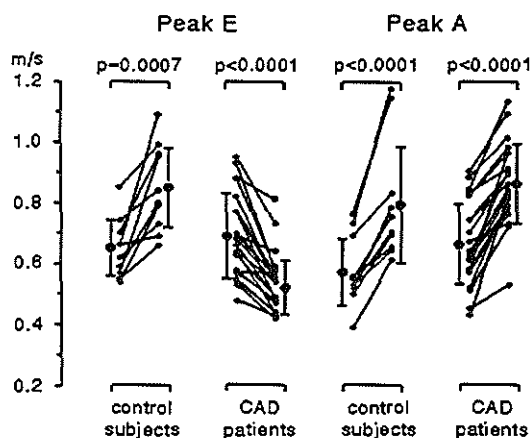


Figure 2: Individual, mean and standard deviation values of average E-wave acceleration rate (E-Acc) and diastolic time velocity integral (TVI_D) obtained at baseline and peak dobutamine from control subjects and patients with CAD.

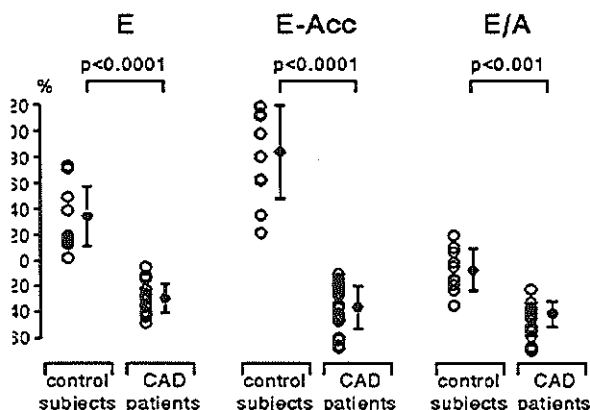


Figure 3: Individual, mean and standard deviation values of the percent change from baseline to peak dobutamine in peak early (E) filling velocity, average E-wave acceleration rate (E-Acc), and early to atrial filling velocity ratio (E/A). Note the levels that distinguished patients with CAD from control subjects.

Although the trends in the response of mitral Doppler indices to dobutamine were different between the 2 groups, there was a considerable overlap in the absolute baseline and peak dobutamine values (Figure 1 and 2). On the other hand there was no overlap in the range of percent change, from baseline to peak dobutamine, between controls and patients for peak E (mean 33%, range 5% to 67% in controls vs -22%, range -11% to -38% in patients; $p < 0.0001$), and E-acceleration (mean 76%, range 22% to 117% in controls vs -40%, range -6% to -55% in patients; $p < 0.0001$) as shown in Figure 3. Overlap in the percent change of TVI_D (mean 21%, range -8% to 73% in controls vs -25%, range 2% to -49% in patients; $p < 0.0001$), occurred in 4 control subjects who had reduction in TVI_D and 2 patients.

Discussion

Several studies described changes of Doppler-derived parameters of either systolic^{5,6} or diastolic^{16,17} left ventricular performance in response to various physiologic and pharmacologic interventions and suggested

that Doppler examination might be an useful adjunct to stress testing. This study describes the effects of high dose dobutamine ($40 \mu\text{g/kg/min}$) on Doppler parameters of left ventricular systolic and diastolic function in a control group of patients with chest pain but low likelihood of CAD and patients with significant single vessel CAD and to assess the utility of this approach in detection of CAD compared to wall motion analysis.

Dobutamine stress test: Hyperkinetic wall motion with increased systolic thickening of normal segments was observed in both groups. Dobutamine-induced new wall motion abnormalities were detected in 7 patients only after addition of atropine. This may be due to continuation of antianginal medication in these patients¹⁸. In the current study the sensitivity of dobutamine-atropine echocardiography for detection of single vessel CAD (61%) is comparable with those reported by Cohen et al¹⁹ (69%) and Mazeika et al²⁰ (50%). The sensitivity was higher for left anterior descending disease. This is in agreement with previous reports of our group²¹.

Doppler aortic flow indices: In this study changes in aortic flow indices with dobutamine showed qualitatively similar responses both in the control subjects and patients with CAD. Dobutamine-induced augmentation of ventricular contractility and reduction in peripheral vascular resistance may explain the increase in aortic velocity and acceleration observed in this study²². The statistically significant lower rise in aortic acceleration in patients compared to control subjects may suggest the proposed high sensitivity of this index in detecting subtle left ventricular dysfunction^{3,4}. Against this concept is the insignificant difference in changes in aortic indices between patients with and without dobutamine-induced wall motion abnormalities. Medications and in particular β blockers may have attenuated the rise in aortic acceleration in CAD patients²³. These findings suggest that regional dysfunction was not severe enough to alter the global function, probably due to a compensatory hyperkinesia in the normal segments. Our findings are in agreement with those of Mazeika et al²⁴ who studied the effect of dobutamine (up to $20 \mu\text{g/kg/min}$) on pulsed-Doppler left ventricular ejection indices and observed similar responses of aortic flow indices to dobutamine in normal subjects and patients with single vessel CAD.

Doppler transmitral flow indices: In control subjects, dobutamine resulted in a uniform and a marked increase in E, A, TVI_D , E-acceleration with no change in E/A ratio or E-deceleration. The mechanism of this augmented diastolic filling may involve: (1) improved myocardial relaxation secondary to a β_1 mediated increase in

intracellular cyclic adenosine 3',5'-monophosphate, which accelerates the rate of calcium reuptake by the sarcoplasmic reticulum and thus stimulates myocardial deactivation process²⁵, (2) enhanced systolic performance augmenting filling by mechanical suction²⁶, (3) increased heart rate which may accelerate myocardial relaxation²⁷.

Abnormalities in Doppler indices of left ventricular filling, such as, reduced E with augmented A and low E/A ratio, have been reported in patients with myocardial ischemia at rest⁹. In the current study the mitral velocity pattern obtained in patients at baseline demonstrated lower E-deceleration and longer isovolumic relaxation period when compared to controls. This pattern, even in the absence of reduced E or E/A, suggests altered relaxation⁹. However, the interpretation of these data may be difficult due to several factors: (1) slower heart rate in patients at baseline, (2) effect of antianginal medications, (3) the overlap of values between the two groups, (4) and finally the nonspecificity of this pattern for CAD²⁸.

In patients with CAD, and in response to dobutamine left ventricular filling was found to be significantly altered in all patients as evidenced by the marked decrease in E, E-acceleration, E/A ratio and TVI_D and increase in A. These findings coupled with similar previously reported alterations in left ventricular filling during acute ischemia induced by different modalities^{2,16,17}, suggest that myocardial ischemia is a possible mechanism influencing diastolic filling pattern in response to high dose dobutamine.

Left ventricular diastolic filling is predominantly mediated by a complex interaction of myocardial relaxation, passive filling properties, and left atrial pressure²⁸. This complicate the interpretation of the alterations in mitral velocity pattern, specially in the absence of simultaneous intracardiac pressure and quantitative left ventricular volume measurements. However, some mechanisms can be proposed to explain such alterations. The reduction in parameters of early filling (peak E and E-acceleration) observed in our patients may be attributed to impaired myocardial relaxation secondary to myocardial ischemia²⁸. This is particularly true in the absence of significant increase in left atrial pressure, due either to increased chamber stiffness or abnormalities in loading conditions²⁹. It is not expected that left atrial pressure will rise during dobutamine as has been previously demonstrated that dobutamine-induced ischemia results in a decrease in stroke volume with no change in pulmonary wedge pressure³⁰.

Increased atrial contribution to filling may have resulted as a compensatory mechanism to reduced early filling or secondary to increased heart rate^{28,29}. In presence of increased heart rate atrial systole may occur during the deceleration slope of early filling resulting in increase in atrial contribution to filling²⁹.

Changes in TVI_D during dobutamine-induced ischemia may reflect a true reduction in stroke volume³⁰ or may be due to shortening of the diastolic filling period secondary to increase heart rate. Against the first assumption is the insignificant change in TVI_S , which theoretically should parallel changes in TVI_D . In agreement with the second assumption is the fact that rapid heart rate considerably shorten diastolic filling time more than the duration of contraction. In our patients, the reduction in diastolic filling time from baseline to peak dobutamine (45%) was significantly higher than the reduction in ejection time (22%).

Limitations of the study: Doppler patterns of left ventricular ejection and filling are influenced by a number of well known factors^{23,28,31-33}. Some of these are particularly relevant to this study. Previous studies have demonstrated that aortic flow indices and early filling indices obtained by Doppler decrease progressively with age^{31,33}. A factor which may have contributed in part to some of the observed abnormalities in Doppler response in our patients. We believe that the abnormalities observed in early filling indices in response to dobutamine reflect true ischemia, and not merely due to the influence of age or medications. We have performed dobutamine stress Doppler echocardiography on patients before and after coronary angioplasty, and found that the Doppler response of filling indices changed towards the normal response after angioplasty³⁴. Changes in heart rate have been shown to significantly alter the Doppler transmitral profile predominantly by increasing atrial contribution to filling³². However, our conclusions were not based on changes of peak A or E/A ratio. In spite of the limitations in Doppler methodology, our results sufficiently dramatic to encourage further investigations in larger population.

Conclusions: Our findings demonstrate that: (1) in patients with low likelihood of CAD high dose dobutamine-stress enhances left ventricular systolic and diastolic performance, as evidenced by the marked increase in Doppler measurements of both ejection and filling dynamics and the hyperkinetic wall motion; (2) changes in Doppler parameters of systolic function with dobutamine stress can not be reliably used to identify individual patients with single vessel CAD; (3) during dobutamine stress

test all patients had an abnormal response of Doppler parameters of early filling.

Thus, it appears that during dobutamine-stress test, an abnormal response of Doppler parameters of left ventricular early filling is a more sensitive marker of significant single vessel CAD than new wall motion abnormalities.

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CHAPTER 7

REPRODUCIBILITY OF DOBUTAMINE-ATROPINE ECHOCARDIOGRAPHY STRESS TEST¹

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Abstract

To assess the reproducibility of dobutamine-atropine echocardiography testing, two studies (1 to 20 days apart [mean 3.3 days]) were performed in 23 patients with stable effort angina pectoris or chest pain. During the study, 20 (87%) patients were receiving beta blockers alone or combined with nitrates or calcium antagonists. Dobutamine was infused at doses of 10 $\mu\text{g}/\text{kg}/\text{minute}$ every 3 minutes up to a maximum of 40 $\mu\text{g}/\text{kg}/\text{min}$ and this maximal dose was continued for 6 minutes. In patients not achieving 85% predicted maximal heart rate or myocardial ischemia, atropine (0.25 - 1 mg) was added and dobutamine continued for another 3 minutes, until either an adequate heart rate was achieved or the test was considered positive. During dobutamine infusion electrocardiographic, echocardiographic, and blood pressure monitoring were obtained in each patient. Side effects including tremor, nausea, palpitation, dizziness, headache, and nonsustained ventricular tachycardia occurred in three patients. The same symptoms, but no ventricular tachycardia, developed during the same stage of the second test. Angina pectoris (eight patients), electrocardiographic changes (six patients), and

¹Echocardiography 1993;10:93-97.

ischemic wall-motion abnormalities (six patients), were observed at the same stage of the two tests. The mean values of heart rate, blood pressure and rate-pressure product were comparable for each stage in duplicate tests. Our data show that pharmacological stress echocardiography using dobutamine-atropine has good reproducibility and provides a useful tool for assessing disease progression and the effects of therapeutic interventions in patients with coronary artery disease.

Introduction

Pharmacological echocardiography stress testing with adenosine, dipyridamole and dobutamine, is increasingly used for identifying patients with coronary artery disease¹⁻¹⁰. In contrast to conventional exercise stress testing¹¹⁻¹², only a few studies exist regarding the reproducibility of sequential pharmacological stress echo¹³, which is relevant when these tests are used to evaluate the efficacy of therapeutic interventions in patients with coronary heart disease. Accordingly, the present study was undertaken to assess the short-term reproducibility of dobutamine-atropine echocardiography testing with regard to time of onset of symptoms, hemodynamic parameters, left ventricular wall-motion abnormalities, and electrocardiographic changes in patients with stable angina pectoris or a high probability of coronary disease.

Methods

Patients: Twenty-three consecutive patients (13 men and 10 women, mean age 62 ± 10 years) with stable effort angina pectoris or chest pain, referred to our laboratory for echocardiography stress testing were enrolled after informed consent was obtained. The presence of coronary heart disease was documented in 21 (91%) of 23 patients by history of a previous myocardial infarction, coronary angiography, or exercise single-photon emission computed tomography perfusion. During the study, 20 (87%) patients were receiving therapy with beta blockers alone or combined with nitrates or calcium antagonists.

Study protocol: In each patient, two dobutamine echocardiography tests were performed at an interval of 1 to 20 days (mean 3.3 days). Clinical condition and therapy remained stable between the two studies.

Dobutamine-Atropine Test: Dobutamine was infused intravenously by an infusion pump with continuous electrocardiographic and

two-dimensional echocardiographic monitoring, using a protocol that included six operative stages organized as follows: 10 $\mu\text{g/kg/minute}$ over 3 minutes (stage 1); 20 $\mu\text{g/kg/minute}$ over 3 minutes (stage 2); 30 $\mu\text{g/kg/minute}$ over 3 minutes (stage 3); 40 $\mu\text{g/kg/minute}$ over 3 minutes (stage 4); 40 $\mu\text{g/kg/minute}$ over 3 minutes (stage 5); and atropine 0.25 - 1 mg (stage 6) that was added on top of dobutamine when the target heart rate or an ischemic end point was not reached⁴. Dobutamine infusion was stopped when the heart rate reached 85% of the age predicted maximal heart rate, or at the onset of new significant electrocardiographic ST depression or elevation, clear echocardiographic wall-motion abnormalities, angina, or major side effects. If the test was strongly positive, in case of side effects or if the heart rate remained increased for longer than 5 minutes after the end of the infusion, an intravenous beta blocker was administered (metoprolol 1 to 5 mg). Blood pressure was measured by cuff sphygmomanometer at the end of each stage of the protocol, and 12-lead ECG was recorded every minute. Rate-pressure product, the time from the beginning of dobutamine infusion to onset of symptoms, wall-motion abnormalities, and ECG changes were evaluated.

Echocardiography: Two-dimensional echocardiographic images were obtained with a commercially available imaging system (Hewlett-Packard SONOS 1000 [Hewlett-Packard, Andover, MA, USA]), and recorded on a connected videotape (Panasonic 6200 VHS) for later playback and analysis. In the baseline studies as well as during each stage, multiple sections, including parasternal long and short axes, apical two- and four-chambers views were obtained when possible. The echocardiograms were independently analyzed off line by two experienced observers unaware of the clinical findings and the study sequence. The judgment of a third observer was obtained in doubtful cases. A test was considered positive if a transient wall-motion abnormality or an extension of a previously asynergic area developed following administration of dobutamine-atropine. Left ventricular wall motion was visually evaluated by two observers, stage by stage, and scored as 1 (normal or hyperkinetic), 2 (hypokinetic), 3 (akinetic), and 4 (dyskinetic) in a 14-segments left ventricular model. A wall-motion score index was calculated by adding the numeric value assigned to each segment and dividing by the number of segments visualized.

Statistical Analysis: Heart rate, blood pressure, rate-pressure product and wall-motion scores were reported as mean values \pm standard deviation. Differences for each stage and between the two tests were

compared using the paired Student's *t*-test. Categorical variables were evaluated with Chi-square test. For statistical significance a value of $p < 0.05$ was required.

Results

Clinical and hemodynamic results: Two sequential dobutamine-atropine tests were performed in all 23 patients. Minor side effects including palpitations, an episode of nonsustained ventricular tachycardia (9 beats), tremor, dizziness or headache were observed in 3 (13%) patients during the first test. In each of these cases, the same side effects, with the exception of ventricular tachycardia, developed at the same stage of the second test. In addition to dobutamine, atropine was given intravenously in 10 (43%) patients at the first test, and in 12 (52%) patients during the second. Beta blocker was administered in 12 (52%) and in 13 (56%) patients at the end of the first and the second tests, respectively (Table I). Heart rate, systolic blood pressure, rate-pressure product at rest and during the other stages did not significantly differ between the two tests (Fig. 1). These parameters progressively and significantly increased during dobutamine-atropine infusion at a similar extent during the two tests. Angina pectoris occurred in 8 (35%) patients at the same stage in the first and the second test, while heart rate, blood pressure, and the double product were comparable in 7 of these patients (Table I).

Electrocardiographic changes: Ischemic ST depression (1 mm or more) and one case of ST elevation were detected in six (26%) patients at the same stage of both tests; these induced ischemic changes were of similar extent and in the same territory for the two tests.

Echocardiographic results: Resting echocardiographic wall-motion abnormalities were identified in ten (43%) patients, all with a history of a previous myocardial infarction. During dobutamine-atropine testing, new and transient dyssynergy occurred, with similar extent and localization, at the same stage of both tests in six (26%) patients, all with documented coronary disease.

In the present study there was disagreement between the two observers for reading the stress echocardiography in 3 (6.5%) of 46 tests. These data are consistent with inter- and intraobserver variability of 91% and 92 %, respectively, as previously tested in our laboratory⁷.

Table 1 Clinical, electrocardiographic, and echocardiographic abnormalities observed in the study population during duplicate dobutamine-atropine echocardiography tests.

	Test I (23 Patients)	Test II (23 Patients)	Agreement (%)
Side effects	3	3	100
Angina	8	8	100
ST depression	5	5	100
ST elevation	1	1	100
Transient dyssynergy	6	6	100
Atropine	10	12	83
Metoprolol	12	13	92

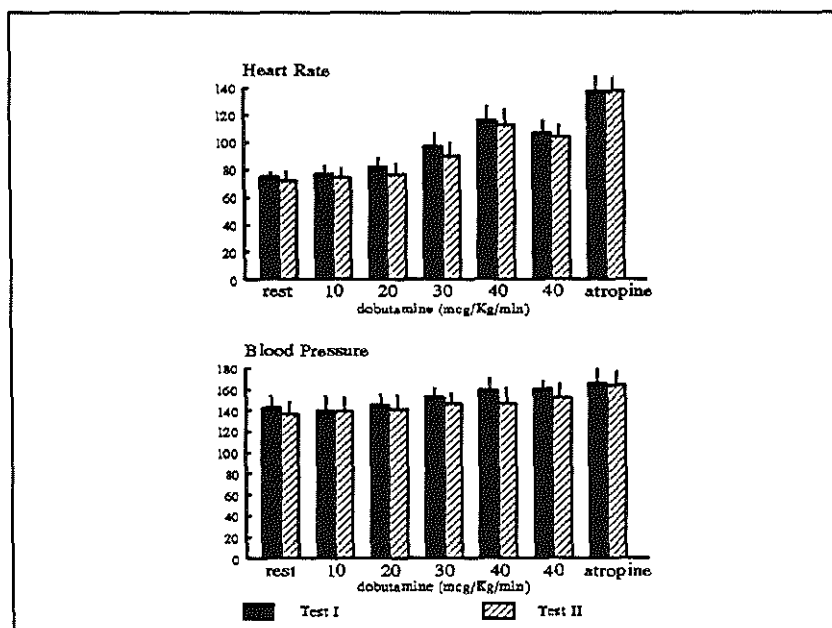


Figure 1. Comparison of mean values of heart rate and systolic blood pressure between dobutamine-atropine echocardiography tests.

Discussion

Two-dimensional stress echocardiography is increasingly used in the evaluation of patients with coronary artery disease. Among the different types of stress proposed, pharmacological stimulation with dipyridamole or dobutamine is largely used in the clinical setting for its well-established safety, and high sensitivity and specificity in detecting single and multivessel coronary disease. The mechanism by which these two drugs induce ischemia is different: dipyridamole¹⁴ mainly by a blood flow maldistribution, with reduction of subendocardial flow in the territory related to the stenotic coronary artery; and dobutamine¹⁵ by a complex stimulation of α_1 , β_1 and β_2 adrenoreceptors, which induces an increase in heart rate, systolic blood pressure and myocardial contractility with consequent marked increase in myocardial oxygen consumption. Reproducibility is the first feature of a stress test that needs to be defined before using the test for assessing efficacy of therapeutic interventions. A high reproducibility is well documented for conventional treadmill and bicycle exercise stress testing but no studies exist regarding dobutamine stress echocardiography. Recently Picano et al¹³ reported good reproducibility of dipyridamole stress echocardiography in patients with effort and rest angina. The reproducibility of a stress test depends on some biological and technical variables: the time course evolution of the disease that influences the threshold of angina; the effects of therapy; and the inter- and intraobserver variability in performing the procedure and interpreting the results. To avoid these problems, we enrolled patients with stable effort angina or chest pain, the two tests were performed at a short time interval, no therapeutic changes were made during the study, and two experienced echocardiographers with good training in stress echocardiography reviewed the examinations. In this study, symptoms, side effects, heart rate, blood pressure, heart-pressure product, and wall motion did not significantly differ for the two tests. However, we must take into account that our data are expressed as mean group values, and some minimal individual differences have been observed in heart rate and systolic blood pressure, particularly because these parameters can be easily influenced by vagal tone and some external factors. This could explain, for example, the different number of patients that needed the addition of atropine for reaching 85% of the predicted maximum heart rate during the first and the second tests.

In conclusion, pharmacological echocardiography stress testing by dobutamine-atropine has good reproducibility and provides a useful tool for assessing disease progression and effects of therapeutic interventions in patients with coronary artery disease.

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CHAPTER 8

REPRODUCIBILITY OF TRANSMITRAL PULSED DOPPLER PARAMETERS OF LEFT VENTRICULAR FILLING DURING DOBUTAMINE STRESS TEST¹

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Abstract

The aim of this study was to investigate the reproducibility of transmitral Doppler parameters of left ventricular filling in subjects undergoing dobutamine stress and to estimate threshold values which can be used as a reference to detect significant changes in Doppler measurements from baseline to peak dobutamine in an individual patient. The study groups included 11 male volunteers and 26 patients with coronary artery disease. Intra and inter-observer tests were performed on 14 randomly selected tracings. The random variation of measurements (beat to beat variations plus random observer error) was estimated at baseline and peak dobutamine both in normals and patients. The parameters studied were: peak early (E) and atrial (A) filling velocities and their ratio (E/A), early filling acceleration (E-AC) and deceleration (E-DC) rates and diastolic time velocity integral (TVI). Intra- and interobserver mean differences were generally small (<5%) with the largest found in the interobserver differences in E-AC (12%) and TVI (7%). The random variation of measurements at baseline were similar in normals and

¹Echocardiography 1994; in press

patients with the smallest (<5%) variation in E and the largest in E-AC (12%) and E/A (8%). There was a significant ($p<0.01$) increase in the coefficient of variation from baseline to peak dobutamine for E (4.5% vs 7.6%), E-AC (11% vs 14.8%) and E-DC (6.5% vs 9.3%) in the patient group. The threshold values were calculated based on the random variation in a single patient and with the assumption that 3, 5 or 8 beats were analyzed at both instances. Conclusions: When Doppler evaluation of left ventricular filling is used during dobutamine stress, the following points should be considered: (a) peak E has the smallest variability among Doppler indices that assess early filling phase, (b) the variability of Doppler measurements of early filling increases with stress intervention in patients with CAD, (c) increasing the number of beats averaged from 3 to 8 reduces the threshold needed to decide significant difference in Doppler measurements between baseline and peak dobutamine by more than the half.

Introduction

Doppler echocardiography is a noninvasive technique capable of providing beat to beat information about left ventricular (LV) filling¹ and has been well validated against other invasive and noninvasive methods^{2,3}. Abnormalities of Doppler indices of LV filling have been demonstrated in patients during ischaemia induced by dynamic exercise⁴, pacing⁵ and dipyridamole stress test⁶ and have been proposed as more sensitive indicators of myocardial ischaemia than systolic abnormalities^{7,8}.

Pharmacological stress testing utilizing dobutamine is increasingly used for the evaluation of the functional significance of coronary artery disease (CAD)^{9,10}. We have previously shown that dobutamine echocardiography has good reproducibility and provides a useful tool for assessing disease progression and the effects of therapeutic interventions in patients with CAD¹¹. The use of the Doppler technique with dobutamine stress, as well as other interventions, is limited by the uncertainty as to whether a change induced by dobutamine is indeed significant or caused by measurement variability.

The reproducibility of the Doppler method is determined by the consistent error (bias) and the random variation of measurements. Differences in bias can be measured with interobserver tests. The overall random variation (beat-to-beat variation plus random observer error) can be estimated by performing serial measurements of consecutive cardiac cycles. Previous studies on the reproducibility of Doppler

measurements of LV filling have been performed in subjects in the resting state^{12,13} and have not defined the reproducibility of Doppler measurements of LV filling during dobutamine stress, or any other stress modalities, or determined the threshold values which constitute a significant difference in Doppler measurements in an individual patient during stress intervention.

The purpose of this study, therefore, is to assess the reproducibility of Doppler indices of LV filling both at baseline and peak dobutamine in normal subjects and CAD patients and to estimate threshold values which can be used as a reference to detect significant changes in Doppler measurements from baseline to peak dobutamine in an individual patient.

Methods

Study population: The study population comprised two groups. Group I consisted of 11 clinically healthy volunteers, all men with a mean age of 41 ± 12 years. All subjects had normal examination, resting electrocardiogram (ECG) and two-dimensional echocardiogram and Doppler and none had history of cardiovascular or any other disease or was on any medication. Group II consisted of 26 patients (22 men and 4 women, with a mean age of 56 ± 10 years) with documented CAD. Twenty two patients had single-vessel disease and 4 had multivessel disease. Sixteen patients were treated with beta blockers, 14 with nitrates and 11 with calcium antagonists. All subjects included were in sinus rhythm.

Study protocol: After giving informed consent dobutamine stress test was performed according to the previously described protocol⁹. Dobutamine was infused starting at a dose of $10 \mu\text{g/kg/min}$, increasing by $10 \mu\text{g/kg/min}$ every 3 minutes to a maximum of $40 \mu\text{g/kg/min}$ which was continued for 6 minutes.

Doppler technique: Doppler signals of the transmitral flow were obtained at baseline and peak dobutamine by an experienced cardiologist using a Hewlett-Packard Sonos 1000 echo apparatus with 2.5 MHz transducer. The velocity profile was recorded from the apical 4-chamber view with the sample volume located between the mitral leaflet tips. Doppler signals with simultaneous ECG were recorded, at least 20-25 beats, on paper at a speed of 50 mm/s.

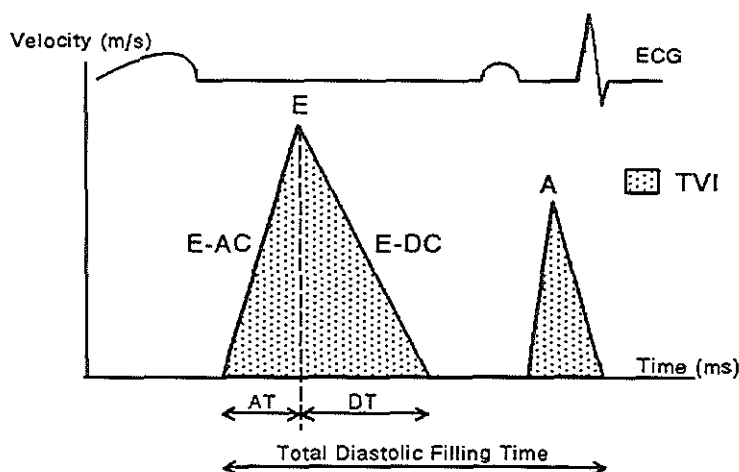


Figure 1: Schematic representation of transmitral flow velocity profile with simultaneous electrocardiogram (ECG), demonstrating Doppler measurements of: A = peak atrial filling velocity, AT = acceleration time, E = peak early filling velocity, E-AC = E wave acceleration rate, E-DEC = E wave deceleration rate, DT = deceleration time, TVI = total diastolic time velocity integral.

Analysis of Doppler data: All Doppler recordings were analyzed by an experienced cardiologist by tracing the maximum velocity envelope. All measurements were performed utilizing an off-line computer, a digitizing tablet (Summagraphics MM961) and a dedicated software¹⁴. The following measurements were obtained from simultaneous Doppler signals of mitral flow and ECG (Figure 1): (1) Indices of early filling: *a.* peak early filling velocity (E); *b.* average early filling acceleration rate (E-AC), calculated by dividing peak E over the time interval from beginning of the flow to peak E; *c.* average early filling deceleration rate (E-DC), calculated by dividing peak E over the time interval from peak E to the time when flow velocity returns to baseline; (2) indices of atrial contribution to LV filling: *a.* peak atrial filling velocity (A); *b.* the ratio between peak early and atrial filling velocities (E/A); (3) diastolic time-velocity integral (TVI) as an index of global LV filling and (4) corresponding heart rate (HR). For each of the Doppler measurements

7 to 8 consecutive cardiac cycles were analyzed to avoid respiratory effect.

Variability of measurements and statistical methods: Intra- and interobserver variability were assessed by analysis of 14 randomly selected Doppler recordings twice by one observer and once by another experienced echocardiographer independently. Differences in observer bias were estimated for every parameter by calculating the mean values of the differences of the paired measurements. The significance of the difference of observer bias was tested using a paired t-test.

Overall random variation (beat-to-beat variation plus random observer error) was estimated by applying one way analysis of variance¹⁵. Random variation was expressed as standard deviation and as a % relative to the mean (coefficient of variation). Coefficients of variation at baseline and peak dobutamine were compared using an F-ratio test.

Based on the number of measurements taken at both instances and with the knowledge of the mean values of respective measurements and the standard deviation of the total random variation, threshold values for statistically significant changes between 2 consecutive Doppler examinations were calculated with an unpaired t-test¹⁶. In this way one can assess whether a change induced by dobutamine is indeed significant (fall outside the range of random measurement variability), for an individual patient. A level of $p < 0.05$ was considered statistically significant.

Results

Intra- and interobserver variability: The means and standard deviations of the intra- and interobserver differences with the mean values, standard deviations and ranges of the measurements obtained from 108 measurements in 14 randomly selected recordings are shown in Table I. Small ($\leq 5\%$) but significant differences in observer bias were found in some Doppler indices. The largest differences, relative to the mean of the measurements, were observed in the interobserver test of E-AC (12%) and TVI (7%).

Random measurement variability: The random measurement variation (beat-to-beat variation plus random observer error) of the respective Doppler parameters estimated at baseline and peak dobutamine in the healthy volunteers and expressed as standard deviation and coefficient of variation are shown in table II. The smallest variations were found in the HR and peak E either at baseline or peak dobutamine. There were

no significant differences in the coefficients of variation of the measurements between baseline and peak dobutamine for all parameters except E-DC. The latter showed significantly larger variations at peak dobutamine compared to that at baseline.

Table I. The results of the intra- and interobserver tests.

parameter	Univariate statistics*			Intra-observer differences		Inter-observer differences	
	mean	SD	range	mean	SD	mean	SD
E m/s	0.653	0.186	0.200-1.04	-0.002	0.029	0.024*	0.043
A m/s	0.652	0.163	0.289-1.01	-0.001	0.029	0.016*	0.042
E/A	1.12	0.542	0.239-1.12	0.003	0.081	0.01	0.143
E-AC m/s ²	8.91	2.44	4.68-16.4	0.478*	1.43	1.08*	2.4
E-DC m/s ²	3.56	1.08	1.54-7.56	0.145	0.544	-0.027	1.04
TVI cm	16.6	4.04	8.01-27.6	-0.6*	1.44	1.15*	1.98
HR b/min	80	26	48-137	0.118	1.31	-0.156	3.78

* p<0.01; * mean values, standard deviation and ranges of 108 measurements; A = peak atrial filling velocity; E = peak early filling velocity; E/A peak early to atrial filling velocity ratio; E-AC average early filling acceleration rate; E-DC average early filling deceleration rate; HR = heart rate; SD = standard deviation; TVI = time velocity integral.

Table II. The random variation of the measurements in the normal subjects at baseline and peak dobutamine.

Normals (n _p = 11)	Baseline (n _b = 81)			Peak dobutamine (n _b = 81)		
	mean	SD	cv (%)	mean	SD	cv (%)
E m/s	0.675	0.03	4.494	0.902	0.047	5.07
A m/s	0.5	0.035	7.66	0.675	0.053	7.83
E/A	1.43	0.141	8.41	1.4	0.149	10
E-AC m/s ²	10.1	1.33	12.2	13.5	1.9	14.4
E-DC m/s ²	4.33	0.313	7.06	5.15	0.526	9.59*
TVI cm	13	0.739	5.65	17.2	0.976	5.54
HR b/min	71	2.34	3.46	99.5	3.55	3.52

* p<0.01 F-ratio test versus baseline. cv = coefficient of variation; n_b = number of beats; n_p = number of patients; SD = standard deviation. Abbreviations of parameters; see Table I.

Table III presents the random measurement variation of the respective Doppler parameters estimated at baseline and peak dobutamine in patients with CAD. At baseline the coefficients of variation of the measurements in patients were similar to those found in normals with the smallest variations found in the HR and peak E. At peak dobutamine, statistically significant increases in the coefficient of variation were observed for E, E-AC and E-DC.

Table III. The random variation of the measurements in patients at baseline and peak dobutamine.

Patients ($n_p = 26$)		Baseline ($n_b = 200$)			Peak dobutamine ($n_b = 198$)		
Parameter	mean	SD	cv (%)	mean	SD	cv (%)	
E m/s	0.671	0.031	4.51	0.516	0.035	7.56*	
A m/s	0.672	0.045	6.91	0.861	0.049	5.88	
E/A	1.03	0.086	7.71	0.607	0.05	8.86	
E-AC m/s ²	10.5	1.29	11	7.56	1.18	14.8*	
E-DC m/s ²	3.18	0.214	6.5	3.12	0.291	9.27*	
TVI cm	17.9	1.01	5.48	13.3	0.832	6.25	
HR b/min	63.2	1.31	2.06	110	2.34	2.23	
* $p < 0.01$ F-ratio test versus baseline. cv = coefficient of variation; n_b = number of beats; n_p = number of patients; SD = standard deviation. Abbreviations of parameters; see Table I.							

Table IV. The percent threshold values for a significant difference in Doppler measurements at a levels of significance $p < 0.01$ and $p < 0.05$ and based on various numbers of averaged beats (3, 5 and 8).

Patients ($n_p = 26$)		% threshold at $p < 0.01$			% threshold at $p < 0.05$		
Parameter	mean	$n_b = 3$	$n_b = 5$	$n_b = 8$	$n_b = 3$	$n_b = 5$	$n_b = 8$
E m/s	0.671	23.3%	13.2%	9.3%	14.1%	9.1%	6.7%
A m/s	0.672	24.1%	13.6%	9.6%	14.5%	9.4%	6.9%
E/A	1.037	31.1%	17.6%	12.4%	18.8%	12.1%	8.9%
E-AC m/s ²	10.5	48.9%	27.7%	19.4%	29.5%	19%	14%
E-DC m/s ²	3.78	30%	17%	11.9%	18.1%	11.7%	8.6%
TVI cm	17.86	22%	12.5%	8.8%	13.3%	8.6%	6.3%
HR b/min	63.2	8.1%	4.6%	3.2%	4.7%	3.1%	2.3%
n_b = number of beats; n_p = number of patients. Abbreviations of parameters; see Table I.							

Threshold values: The threshold values, expressed as percentages, for a significant difference in 2 consecutive Doppler examinations, i.e. baseline and peak dobutamine, are shown in Table VI. These values are calculated at two different levels of significance ($p < 0.01$ and $p < 0.05$) and for various numbers of averaged beats (3, 5 and 8). The largest threshold values, calculated on the consideration of 8 beats either at baseline or peak dobutamine, were found in E-AC, E-DC and E/A. Table VI also shows that threshold values increase progressively with the decrease in the numbers of beats considered, as expected.

Discussion

Dobutamine is a potent inotropic agent that causes a dose-dependent increases in HR, cardiac contractility, arterial pressure and oxygen consumption with a slight change in cardiac filling pressures^{17,18}. In a normal heart these changes are associated with an increase in the speed of LV relaxation which augments filling¹⁹. The expected Doppler findings would be an increase in transmitral flow velocities and an increase in early filling acceleration²⁰. On the other hand, demand ischaemia associated with inotropic stimulation would result in no change or a decrease in the speed of LV relaxation. In this instance peak mitral early filling velocity would decrease in proportion to the slowing in relaxation while late filling velocity will increase partly due to the increase in HR and partly as a compensation to maintain LV filling^{21,22}. Therefore, the addition of Doppler evaluation of LV filling to electrocardiographic and wall motion analysis would be of significant clinical importance.

Can Doppler echocardiography effectively monitor the effect of dobutamine on parameters of LV filling in individual patients? To answer this question, two factors should be considered: (a) the reproducibility of Doppler parameters of LV filling including measurement variability, and (b) the magnitude of the change of Doppler parameters after dobutamine. Only if the serial changes are large enough and fall outside the range of measurement variability should the changes be considered significant. We have recently reported the effect of high dose dobutamine stress on Doppler indices of LV filling in healthy subjects and patients with CAD before and after coronary angioplasty²². Our findings demonstrated a significant reduction in early filling indices in response to dobutamine in patients with CAD before angioplasty compared with a significant increase in the same

indices in normal subjects. Furthermore, the response of early filling indices changed toward the normal response after angioplasty.

The reproducibility of the Doppler method depends on 2 determinants: (a) the consistent error (bias); which itself cannot be measured because the true value of the measurement is unknown, but differences in observer bias can be estimated with intra- and interobserver tests, and (b) the random variation of measurements; which can be estimated by taking consecutive measurements in a number of patients.

The overall random variation of the measurements is usually the result of the interplay of several factors. These include: (a) beat-to-beat variability of the measurements which can be due to variations in HR, respiration or variation in the position of the sample volume with changing in the motion of the heart or the patient position, and (b) observer error which introduced by the observer measuring the Doppler recordings and can be due to factors related to adjustment of the Doppler instrument or the method of obtaining or analyzing the recordings. In fact we did not try to investigate the different sources of variability independently, rather we chose to imitate a routine clinical stress testing, in which one observer obtains and analyzes the recordings according to the standard method in our laboratory.

Consistent error (bias): The results of the intraobserver test showed that intraobserver differences were small ($\leq 5\%$) for the Doppler parameters studied. Interobserver differences in bias were $\leq 5\%$ in the measurements of E, A, E/A and E-DC, while the largest differences were found in the measurements of E-AC (12%) and TVI (7%). Since E-AC and TVI are dependent on the definition of the beginning and ending of velocity curve, it seems possible that poor-definition of these points due to the wall filter of the Doppler machine, specially at high HR, was the reason for the relatively large differences in the measurements of these indices.

Random measurement variability: The random variation of the Doppler parameters at baseline were similar in normals and CAD patients. The smallest ($< 5\%$) variations were found in the measurements of peak E. Whereas the largest variations were observed in the measurements of E-AC both in normals (11%) and CAD patients (12%). Of interest, was the relatively large variability (8%) of the E/A, which is commonly used in the Doppler assessment of LV filling. This may be explained by the fact that E/A is calculated from 2 velocities with their own inherent variability.

Since previous studies on the reproducibility of Doppler transmitral flow indices were performed in the resting condition^{12,13,16}, we decided to test if the variability of the measurements changes with stress. When

the coefficients of variation of the Doppler measurements in the healthy volunteers were compared between baseline and peak dobutamine, only E-DC showed statistically significant greater variability at peak dobutamine (9.59%) than baseline (7.06%). Increased HR results in a shortened diastasis and loss of separation between E and A, and consequently the point at the end of the descent of the early diastolic velocity will not be on the baseline. This may result in greater variations in the measurement of deceleration time and consequently in E-DC.

Patients with CAD had statistically significant larger variations in E, E-AC and E-DC, indices of early filling, at peak dobutamine compared to variations at baseline. The larger variations in E, E-AC and E-DC at peak dobutamine in CAD patients compared to normals can be explained by the fact that the magnitude of changes in mean values, from baseline to peak dobutamine, were smaller in CAD group. Therefore, percent wise, the difference in coefficient of variation will be magnified. In addition, calculations of E-AC and E-DC are dependent on measurements of their corresponding time intervals (acceleration time and deceleration time, respectively). Therefore, technical difficulties in the definition of the beginning and ending of E wave velocity curve at high HR may have contributed, at least in part, to the large variations in these parameters. Several factors are known to independently influence early filling velocity²³. Among these is changes in HR. It is noteworthy that the coefficient of variation in HR in CAD patients was not different between baseline (3.46%) and peak dobutamine (3.52%). Therefore the observed increase in the coefficient of variation during dobutamine can not be explained by increase in HR variation. Finally, our patients were older than the normals, on a variety of antianginal medications, and 65% of the patients developed new wall motion abnormalities with dobutamine. Factors which may have contributed to the variability of the measurements. However, we are not aware of studies addressing the independent influence of such factors on the variability of Doppler measurements.

Threshold values: In order to relate our data to clinical practice, we calculated the statistically significant thresholds needed to decide whether a change in Doppler measurements induced during dobutamine stress test is indeed significant. The threshold differences are dependent on the number of measurements taken at baseline and peak dobutamine and the significance level. Several studies examining the value of Doppler parameters of LV filling with stress interventions in the diagnosis of CAD were performed on the basis of analysis of 3^{24,25}, 5²⁶

or 4 to $8^{27,28}$ cardiac cycles. It is clear from table VI, that if one uses the average of 3 beats in Doppler measurements during stress intervention, only changes in E; for example, greater or lesser than 23% can be considered as being significant (at a level of significance $p < 0.01$) change due to the intervention. Thus we run the risk of overlooking a significant change that does not exceed this rather high threshold. Increasing the number of beats analyzed to 8 reduces the threshold on all cases by more than a factor of 2. Finally, it should be realized that the coefficient of variation and the threshold values might be valid only around the mean values of the parameters estimated in this study.

Conclusions: When Doppler evaluation of LV filling is used during dobutamine stress, the following points should be considered: (a) peak E has the smallest variability among Doppler indices that assess early filling phase of diastole, (c) the variability of Doppler measurements of early filling increases with stress intervention in patients with CAD, (d) increasing the number of beats averaged from 3 to 8 reduces the threshold needed to decide significant difference in Doppler measurements between baseline and peak dobutamine by more than the half.

Acknowledgment: We gratefully acknowledge Eric Boersma MS, for the valuable statistical advice.

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CHAPTER 9

DISCUSSION AND CONCLUSIONS

Dobutamine-atropine stress testing closely mimics exercise physiology because it can be performed in an incremental stepwise manner equivalent to the stages of exercise protocol, thereby having the potential to detect an ischaemic threshold. Dobutamine stress testing with or without the addition of atropine has been combined with electrocardiography (ECG),¹ myocardial perfusion scintigraphy,² magnetic resonance imaging,³ and echocardiography,^{4,5,6} for the evaluation of patients with coronary artery disease (CAD). Its combination with Doppler⁷⁻⁹ has also attracted recent interest. The dobutamine stress testing is increasingly applied for the diagnosis of CAD,^{10,11} assessment of revascularization procedures,^{12,13} identification of myocardial viability,¹⁴ and risk stratification in patients after myocardial infarction,^{1,15} and in those undergoing major vascular surgery.¹⁶ The application of dobutamine stress echocardiography and Doppler for the detection of CAD and assessment of coronary angioplasty (PTCA) will be discussed in details.

Diagnosis of myocardial ischaemia

Table I summarizes results of studies from our laboratory^{5,11,18,25} and those from others,^{4-6,17,19-24} that have utilized the assessment of regional wall motion during dobutamine stress echocardiography for the diagnosis of CAD. These studies confirm the ability of dobutamine echo to detect the presence of significant CAD (>50% diameter stenosis) with an overall sensitivity ranging from 54 to 96% and specificity ranging from 60 to 95%. Close analysis of the data derived from these studies identifies several observations of important clinical implications.

(1) Comparison of dobutamine and other stress modalities: Direct comparison of dobutamine and dipyridamole stress echo testing in the same patients have been conducted in few studies.^{17,18,21} In one study from our group, the sensitivities and specificities of dobutamine and dipyridamole stress echo for the detection of myocardial ischaemia were similar.¹⁸ On the other hand, the results of the other studies were in favour of dobutamine echocardiography.^{17,21} Dobutamine echo has also

been shown to be superior to adenosine echo.^{17,19} In our experience²⁶ as well as others,²⁰ dobutamine echo was comparable in efficacy of detecting CAD with exercise stress echo.

(2) *Dobutamine stress Echo vs myocardial perfusion scintigraphy:* We and others have shown equivalent levels of sensitivities and specificities, and a reasonable agreement between the two techniques for detection of myocardial ischaemia, specially in absence of resting wall motion abnormalities (WMA).^{11,19}

(3) *ECG changes and chest pain as markers of ischaemia during dobutamine stress testing:* The diagnosis of myocardial ischaemia based on ECG changes or the development of chest pain during dobutamine stress testing was generally associated with a considerably low sensitivity, although the specificity was consistently high.^{5,6,17,19} The reduced sensitivities of dobutamine stress ECG compared to those usually reported with exercise stress testing probably reflect a lower cardiac work load during dobutamine stress than may be achieved with exercise.¹⁹ The use of WMA as an end point and the continuation of antianginal medications are also factors that have been suggested to reduce the sensitivity of ECG changes or angina during pharmacologic stress testing.⁶

(3) *Factors influencing the interpretation of stress echocardiography:*

- Dobutamine stress echo is more sensitive in detecting myocardial ischaemia in patients with multivessel coronary disease than in those with single vessel disease.^{3,6,19,22,24,25}
- The relation between the severity of coronary stenosis measured by quantitative angiography and stress-induced WMA detected by dobutamine echo has also been investigated. Segar et al⁴ demonstrated that dobutamine stress echo is equally sensitive for the detection of CAD in the three major coronary arteries. They also showed that the correct assignment of WMA to coronary lesions is improved when evaluation was confined to lesions with a minimal luminal diameter <1 mm. Similarly, Salustri et al,²⁵ reported that the sensitivity of dobutamine echo for the detection of CAD was higher in patients with diameter stenosis >70% than in those with diameter stenoses in the range of 50 to 70% or <50%.
- The addition of resting WMA, as a criterion for the presence of CAD, to the development of dobutamine-induced WMA have been reported

to increase the sensitivity of dobutamine stress echo.¹⁸ However, the presence of resting WMA adversely affect the specificity of the test.^{23,4}

Table I: Studies using dobutamine stress echocardiography for the diagnosis of CAD.

Author	Stress	Subjects		Sensitivity (%)				Spec. (%)
		Tot.	CAD	SVD	MVD	NRWM	Overall	
Martin ¹⁷ (1992)	DOB	40	25				76	60
	DIP						56	67
	ADN						40	93
Salustri ¹⁸ (1992)	DOB	46	28				57	78
	DIP						64	89
Marwick ¹⁹ (1993)	DOB	97	59	84	86		85	82
	ADN			52	64		58	87
Cohen ²⁰ (1993)	DOB	52	37	75	95		86	87
	SBE			63	90		78	87
Previtali ²¹ (1993)	DOB	80	57	62	88		79	83
	DIP			33	88		60	96
Cohen ²² (1991)	DOB	70	51	69	100		86	95
Sawada ⁶ (1991)	DOB	103	81	81	100	89		85 [#]
Marcovitz ²³ (1992)	DOB	141	109	95	97	87	96	66 91 [#]
Mazeika ²⁴ (1992)	DOB	50	36	50	75		78	93
Segar ⁴ (1992)	DOB	85	63			90	95	82 86 [#]
McNeill ⁵ (1992)	DOB	80	47				70	88
Salustri ²⁵ (1992)	DOB	52	37	40	70		54	80
Marwick ¹⁰ (1993)	DOB	217	142	66	77		72	83
Forster ¹¹ (1993)	DOB	21				75		89

[#] = specificity in patients with normal resting wall motion.

ADN = adenosine, CAD = number of patients with significant coronary disease (>50% diameter stenosis), DIP = dipyridamole, DOB = dobutamine, MVD = multivessel coronary disease, NRWM = patients with normal resting wall motion, Spec. = specificity, SVD = single vessel coronary disease, SupBE = supine bicycle exercise, Tot. = total number of subjects.

- Difficulties in the interpretation of stress echocardiography for the presence of myocardial ischaemia occur in patients with previous myocardial infarction and severe hypokinesia or akinesia at rest.^{11,25}

Controversy exist, whether the worsening of akinesia, becoming dyskinesia during stress, represents myocardial ischaemia or mainly a nonischaemic mechanical event.²⁷ Recently, we studied 20 patients, with previous myocardial infarction and resting regional akinesia, using simultaneous two-stage (low- and high-dose) dobutamine stress echocardiography and myocardial perfusion scintigraphy.²⁸ We demonstrated that, in the absence of improvement in wall thickening with low-dose dobutamine, the echocardiographic pattern of an akinetic segment at rest, becoming dyskinetic during peak stress, does not represent myocardial ischaemia.

- Antianginal medications, in particular β -blockers, may adversely influence the diagnostic accuracy of dobutamine stress testing. Recently, we demonstrated that β -blockers blunt the chronotropic effect of dobutamine and decrease the incidence of myocardial ischemia as indicated by the reduced incidence of new WMA or ST changes in patients on β -blockers than after washout of the drug.²⁹ However, with the use of our "standard" dobutamine-atropine protocol (reported in Chapter 3), it was possible to overcome the lack of chronotropic effect in such patients and to equalize the detection of myocardial ischaemia in patients on and off β -blockers.²⁹
- Potential limitations for the widespread use of stress echocardiography remain the high degree of operator dependency, which necessitates the availability of a skilled and experienced operator-interpreter, to obtain an accurate test and the subjective analysis of WMA. Until now there is no standard objective criteria for the interpretation of the stress echo results. Quantitative approaches for analysis of regional wall motion have been attempted.^{30,31,32} These approaches require a user-interactive system in which the operator identifies the endocardial border in diastole and systole and then measurements are made by computer. Therefore, the operator dependence is still retained in this form of analysis. In addition, there are great difficulties in establishing a normal range for systolic wall thickening because of the high variability between subjects and between segments and levels within the LV and limited image quality by endocardial dropout in some patients using the transthoracic approach.³²

Assessment of patients undergoing PTCA

The main goal of revascularization therapy is to relief ischaemia and improve prognosis in CAD patients, therefore, functional testing is often

needed to identify objective clinical improvement. Wall motion analysis during dipyridamole³³ or exercise^{34,35} stress echo allowed the identification of a successful PTCA by detecting resolution of stress-induced WMA that was present before the intervention (Table II). We introduced the use of dobutamine-atropine stress testing in this clinical situation and proved the usefulness of the test in detecting the reduction in myocardial ischaemia early after PTCA (Chapter 4).¹² Recent reports confirmed our findings.¹³

Table II Stress echo for the evaluation of patients undergoing PTCA.

Author	Stress	Patients*	Time [#]	Stress-induced WMA	
				pre-PTCA	post-PTCA
Picano ³³ (1989)	DIP	63	1 to 3 days	58	16
Broderick ³⁴ (1990)	TME/UpBE	36	28 ± 26 days	25	12
Fioretti ³⁵ (1992)	UpBE	23	4 weeks	13	2
McNeill ¹² (1992)	DOB/A	28	within 3 days	20	4
Akosah ¹³ (1993)	DOB	35	1 to 2 days	31	3

* = angiographically successful PTCA, # = timing of the post-PTCA test.
DIP = dipyridamole, DOB = dobutamine, DOB/A = dobutamine plus atropine,
TME = treadmill exercise, UpBE = upright bicycle ergometer, WMA = wall motion abnormalities.

The timing for the assessment of the functional improvement after PTCA is an important consideration. Some investigators suggested that the detection of early restenosis may be missed if stress testing is performed soon after PTCA, and therefore some delay may permit better prediction of long-term success.³⁴ Others, supported performing stress echo testing early after PTCA so that important baseline information can be available for later comparison and thus allow full assessment of the effects of the procedure.^{12,13,33} Pharmacological stress testing with dipyridamole or dobutamine, unlike exercise, can be performed early after PTCA even while the patient is still at bed rest (Table II). Another point in favour of applying the pharmacologic type of stress early after PTCA is its ability to stratify the response not only on the basis of associated ECG changes (indicating transmural involvement), and spatial circumferential extent but also by providing the timing of occurrence of WMA during the test.^{13,33}

The persistence of a positive stress echo test after PTCA is another important consideration. Several explanations have been suggested for

such an observation. One explanation was based on the poor correlation between percent luminal reduction and regional flow reserve, leading to a disparity between a residual stenosis which appears angiographically insignificant but remains functionally important.³³ Another explanation is the possibility of early post-PTCA restenosis which could be insignificant at the time of post-PTCA angiography. This explanation is supported by the findings of Picano et al,³³ who demonstrated that all patients with recurrent angina and WMA during the early post-PTCA dipyridamole stress test had angiographic evidence of restenosis of the dilated vessel in the long-term follow up. The phenomena of myocardial hibernation or stunning have also been suggested as an alternative explanation.³⁶ Finally, persistent positivity in a remote region from the territory of the dilated artery may indicate that dilatation of such a "functionally dominant" artery resulted in unmasking of another lesion which was originally less severe.³³ Further studies are needed to evaluate the clinical importance of a persistently positive stress echo testing after angiographically successful PTCA.

Reproducibility of stress echo testing

Reproducibility is a major feature of a stress test that needs to be defined when using the test for assessing efficacy of therapeutic interventions. Sources of error in repeat echo studies include the instability of the testing routine and equipment, patient variability and observer variability both in performing the procedure and interpreting the results. At the Thoraxcentre, the inter- and intraobserver agreement for the interpretation of exercise echo is 91% and 92%, respectively.³⁷ In Chapter 7, we reported an excellent short-term reproducibility of dobutamine-atropine stress testing with regard to, time of onset of symptoms, haemodynamic response, and the frequency of the induction of ischaemia (WMA, ECG changes and angina).³⁸

Assessment of global LV systolic function using Stress Doppler-echocardiography for the diagnosis of myocardial ischaemia

There have been few studies examining the utility of Doppler assessment of aortic flow indices during stress for the detection of CAD. Table III summarizes findings from previous studies using exercise Doppler-echo for the detection of CAD.³⁹⁻⁴² In aggregate, these studies demonstrated that changes in aortic flow indices during exercise tended

to distinguish, as a group, between healthy subjects and patients with CAD. They all confirmed that the Doppler technique appeared to be most helpful in identifying patients with multivessel CAD.

Table IV summarizes findings from previous studies using dipyridamole⁴³⁻⁴⁶ or dobutamine⁷⁻⁹ as stress agents in conjunction with Doppler assessment of transaortic flow for the detection of CAD. Unlike the exercise Doppler studies, findings from dipyridamole Doppler studies were conflicting. Two studies^{43,45} demonstrated that changes in Doppler systolic indices during dipyridamole infusion could distinguish between healthy subjects and patients with CAD. Whereas, the other studies^{44,46} indicated that Doppler-determined changes in systolic indices during dipyridamole were insensitive in detecting patients with significant CAD.

The use of Doppler assessment of global LV systolic function during dobutamine stress testing has recently been attempted.⁷⁻⁹ Mazeika et al⁷ studied the effect of dobutamine (up to 20 $\mu\text{g/kg/min}$) on pulsed-Doppler LV ejection indices and observed similar response in normal subjects and patients with CAD and a blunted response only in 6 patients with WMA in ≥ 3 segments all of whom had multivessel disease. Using continuous wave Doppler during high-dose dobutamine stress (up to 40 $\mu\text{g/kg/min}$), we reported similar responses of Doppler-derived LV ejection indices in healthy subjects and patients with significant single vessel CAD, and a blunted response in patients with multivessel disease (Chapters 5 and 6).^{8,9} Furthermore, we demonstrated that the response of Doppler ejection indices to high-dose dobutamine stress was the same before and early after PTCA (Chapter 5).⁸

Feasibility and limitations of the technique: Using the suprasternal or the apical approaches, a high success rate for Doppler recording of the aortic velocity curve has been reported.⁴³⁻⁴⁶ In our studies (Chapters 5 and 6), using the nonimaging continuous wave transducer from the suprasternal notch window, we were able to obtain adequate Doppler recordings of the aortic velocity curves in 53/57 patients (93%) in both studies. Several technical considerations concerning Doppler measurements of the ascending aortic flow variables during stress are worthy of emphasis, among which:

(1) The potential problem of not maintaining the angle between the ultrasound beam and the long-axis of the blood flow during peak stress due to movement of the aortic root during hyperdynamic contractions and hyperventilation.^{40,47} This problem would affect the absolute

velocities but would not affect the percent change from baseline to peak stress, and therefore does not affect any of our conclusions.

(2) The effect of respiration on both the quality of Doppler recordings and the actual measurements of aortic velocity and time intervals.⁴⁸ To avoid this problem, we obtained measurements from 7 to 8 consecutive beats with the clearest velocity envelop and averaged the results.

(4) A considerable number of our patients were receiving antianginal therapy including β blockers, which have been shown to blunt the response of aortic velocity and acceleration.⁴⁹ In the study in Chapter 5, medications were not changed during studies (before and after PTCA), thus, this should not affect our results.

(5) Finally, it has to be noted that Doppler derived systolic parameters assess the global LV function, therefore, WMA limited to a small number of LV segments may not influence the global LV performance.

Despite these limitations, the use of Doppler approach to quantitate the global LV performance remains attractive. First, unlike conventional use of echo imaging of cardiac structures, with the possible deterioration of image quality due to emphysema, for example, Doppler examination avoids this limitation. This is particularly true when using the small non-imaging continuous wave transducer from the suprasternal position. Second, the use of Doppler derived flow velocity and acceleration as indicators of global systolic performance is not based on geometric assumptions regarding the shape of the left ventricle but rather based on haemodynamic considerations.⁵⁰

Reproducibility of Doppler-derived aortic flow velocity measurements

Data on reproducibility of Doppler aortic flow velocity measurements obtained by nonimaging transducer in normal subjects have been reported. Hatle and Angelsen⁵¹ reported reproducibility data in 16 subjects for Doppler ejection measurements performed within minutes of each other in each subject. The mean coefficient of variation was 5.9% for peak velocity, 6.7% for TVI and 15.1% for acceleration. These investigators concluded that changes in flow velocity of 20 to 25% represent true haemodynamic changes. Gardin et al⁵² studied 10 normal subjects in order to establish the intraobserver, interobserver and day-to-day variability in Doppler aortic flow measurements. They found that if one were to set the mean \pm 2 standard deviations as a range beyond which a measurement difference would be significant, a difference of

10% in TVI, 11% in ejection time, 13% in peak velocity and 17% in acceleration time would suggest a significant haemodynamic change.

Assessment of global LV diastolic function using stress Doppler-echocardiography for the diagnosis of myocardial ischaemia

(1) Abnormal Doppler LV filling pattern at rest, in patients with CAD: Three different patterns of transmitral velocity profile have been described in patients with CAD.⁵³⁻⁵⁸

- Reduced LV early filling: This pattern is described in patients with impaired relaxation, as evidenced by increasing time constant of relaxation, and normal or slightly elevated pulmonary artery wedge pressure.^{53,54} The transmitral velocity profile may show, prolonged IRP and E-wave DT; decreased peak E velocity, mean E-wave acceleration rate and E/A ratio; and increased peak A velocity.⁵³⁻⁵⁶ This pattern has also been described during balloon occlusion of the coronary arteries during PTCA.^{57,58}

- Restricted LV filling: This pattern is described in patients with increased chamber stiffness, as evidenced by increasing chamber stiffness constant,⁵⁴ and those with elevated pulmonary capillary wedge pressure, marked symptoms, left atrial enlargement, and impaired LV relaxation.⁵³ The transmitral velocity profile may show; increased E velocity and E/A ratio; shortened E-wave DT and IRP; and reduced A velocity.^{53,54}

- "Pseudonormal" LV filling: This pattern is noted in patients with impaired relaxation and increased left atrial pressure.⁵³

(2) Abnormal Doppler LV filling pattern during stress-induced ischaemia: There have been few clinical studies that described abnormalities of LV diastolic filling in patients during transient ischaemia provoked by exercise,⁵⁹⁻⁶¹ pacing,⁶²⁻⁶⁴ or dipyridamole stress testing^{44,46,64,65} (Tables V, VI and VII, respectively).

Studies in table V demonstrated abnormal LV diastolic filling in response to exercise, however, the types of filling patterns have varied. Unlike the studies performed with exercise, pacing-induced ischemia was associated with changes in the Doppler pattern of transmitral flow consistent with the pattern of impaired relaxation.

Most studies^{46,64,65} on dipyridamole-stress Doppler for the assessment of LV filling dynamics have reached the conclusion that the response of Doppler diastolic indices is similar in healthy subjects and patients with significant CAD (Table VII). Little information is available regarding

the changes in LV filling dynamics in response to dobutamine stress testing. In Chapter 6, we described the effects of high-dose dobutamine (up to 40 $\mu\text{g/kg/min}$) on Doppler parameters of LV diastolic function in a control group of patients with chest pain but a low likelihood of CAD and patients with significant single vessel CAD and assessed the utility of this approach in detection of CAD compared to wall motion analysis. Our findings demonstrated a significant increase in Doppler parameters of LV filling in response to high-dose dobutamine in patients with low likelihood of CAD; and a significant decrease in early filling indices in all patients with significant single vessel CAD.

(3) *Doppler LV filling pattern in patients undergoing PTCA*: The use of Doppler transmitral flow velocity recordings to detect improvements in LV diastolic filling following PTCA has been attempted at rest (Table VIII).^{8,66-69} Three of the five studies in Table VIII demonstrated early improvement in LV filling after PTCA.⁶⁷⁻⁶⁹ Our findings, as well as others, demonstrated unchanged resting diastolic parameters early after PTCA, compared to before PTCA.^{8,66} Differences in patient populations and methodology (Table VIII) may explain these discrepancies.

Studies of LV filling during cardiac stress testing after PTCA have been limited to radionuclide angiography.⁷⁰ In Chapter 5, we presented the initial experience in the use of Doppler assessment of LV filling in conjunction with high-dose dobutamine stress testing in patients undergoing PTCA. Our findings demonstrated improvements after PTCA, in the response of early filling indices to dobutamine, as evidenced by changing the direction of the response of these parameters from decreasing before PTCA to increasing after PTCA.⁸

Reproducibility of Doppler transmitral flow velocity measurements

Previous studies on the reproducibility of pulsed-Doppler transmitral flow velocity measurements have been performed in subjects at rest.⁷¹⁻⁷³ Data from these studies suggested that: (a) the technical and biological sources of variability are generally small for early filling indices, whereas, day-to-day variability is relatively large for parameters of atrial filling;⁷¹ (b) the commonly used E/A ratio appears to be able to detect only changes greater than 44% with a confidence probability of 0.95 in an individual patient;⁷² (c) that abnormal transmitral flow patterns in patients with CAD, persist unchanged in the absence of therapeutic intervention.⁷³

The dramatic differences in the response of Doppler transmitral filling indices to dobutamine stress; between healthy subjects and patients with CAD and between patients before and after PTCA (Chapters 5 and 6); encouraged as to test the reproducibility of the Doppler measurements both at rest and peak dobutamine and to estimate threshold values which can be used as a reference to detect significant changes in these measurements from baseline to peak dobutamine in an individual patient (Chapter 8). Our findings demonstrated that: (a) intra- and interobserver mean differences were generally small; (b) the random variations of Doppler measurements at rest (beat-to-beat variations plus random observer error) were similar in healthy subjects and patients with CAD; (c) the variability of Doppler measurements may increase with stress intervention in patients with CAD; (d) increasing the number of beats averaged from 3 to 8 reduces the threshold needed to decide a significant difference in Doppler measurements between baseline and peak dobutamine by more than the half.⁷³

In addition to the reproducibility of the technique, a wide variety of physiologic and pathologic variables may be considered as confounding factors in the interpretation of Doppler transmitral filling velocities (Chapter 2). The influence of such factors on our findings has been discussed in Chapters 5 and 6.

SUMMARY AND CONCLUSIONS

Since the introduction of dobutamine to the field of stress echocardiography testing, efforts have been directed to assess the feasibility, safety and diagnostic accuracy of the test; to improve the sensitivity; and to evaluate the applicability of the test in different clinical situations for the evaluation of patients with CAD. This thesis aimed mainly at testing different methods that may improve the sensitivity of the dobutamine stress testing; and assessing the utility of the test in the assessment of patients undergoing PTCA. This was achieved by: (a) modifying the dobutamine stress protocol by addition of atropine (Chapter 3); (b) adding Doppler examination of the global LV systolic and diastolic function to the conventional analysis of regional wall motion during the dobutamine stress test (Chapters 5 and 6); (c) testing the reproducibility of echocardiographically detected WMA and Doppler measurements of LV diastolic filling during dobutamine stress testing (Chapters 7 and 8); and (d) evaluating changes in ECG, regional wall motion, and Doppler measurements of global LV systolic and diastolic function during high-dose dobutamine stress testing before and early after PTCA (Chapters 4 and 5).

The results reported in this thesis confirm the superiority of dobutamine-induced WMA, as a marker of myocardial ischaemia, over ECG changes or the development of chest pain. The addition of atropine to dobutamine stress echocardiography increases the sensitivity of the test for detection of CAD without loss of specificity or increase the incidence of side effects. This is particularly useful in patients undergoing dobutamine stress test without discontinuation of antianginal medications, specifically β blockers.

Dobutamine-atropine stress echocardiography is also useful in identifying objective manifestations of reduction in myocardial ischaemia, early after PTCA. In our institution, the reproducibility of dobutamine-atropine stress testing is excellent. A factor which makes the test to be a useful tool for assessing disease progression and effects of therapeutic interventions in patients with CAD.

The addition of Doppler examination of aortic flow velocity during dobutamine stress testing is not useful in identifying individual patients with CAD. On the other hand, the addition of Doppler examination of transmitral flow velocity during dobutamine stress testing, appears to add useful indicators of myocardial ischaemia which may be more sensitive

than WMA. Furthermore, Doppler evaluation of LV diastolic filling during dobutamine stress testing, before and after therapeutic interventions, appears to be useful in predicting beneficial effect of the intervention. However, when Doppler examination of LV filling is to be used during dobutamine stress, a reproducibility study is necessary to estimate threshold values (based on the number of beats to be averaged) which can be used as a reference to detect significant changes in Doppler measurements from baseline to peak dobutamine in an individual patient.

Despite the fact, that dobutamine stress testing is being increasingly applied in a wide variety of clinical applications, further research is needed to clarify some related problems. First, we are not aware of studies testing the inter-observer variability in the interpretation of stress echo results between different echocardiography laboratories. Such studies may contribute in establishing the reliability of the technique as a practical tool in the noninvasive evaluation of patients with CAD.

Second, controversy still exist in the interpretation of dobutamine-induced worsening of WMA that existed at rest. Should we consider severe hypokinesia or akinesia which become dyskinesia during stress as an indication of myocardial ischaemia or as a nonischaemic mechanical event? This is an important clinical topic which requires further evaluation.

Third, simple and reproducible methods for quantification of LV volumes or segmental wall thickening are lacking. With newer automated contour-detection equipment, trans-esophageal approach, and the technology of three dimensional reconstruction of echocardiographic images, quantitative analysis may become easier and more widely applicable.

In spite of the limitations in Doppler methodology, dobutamine stress testing should not be limited to the echocardiographic evaluation of wall motion, but rather expanded to include assessment of haemodynamics by means of Doppler examination of LV systolic and diastolic function.

Table III. Studies evaluating the value of Doppler ejection parameters during exercise stress testing for the detection of CAD and risk stratification after myocardial infarction.

Author	Technique	Subjects		Findings
		N	pts.	
Bryg ³⁹ (1986)	TME, PWD	20	17	- \uparrow AoV > 80% in N and pts. with single vessel disease and normal LV function - \uparrow AoV < 80% or \downarrow AoV in pts. with more severe CAD and resting LV dysfunction
Mehdirad ⁴⁰ (1987)	TME, PWD	14	14	- greater \uparrow in AoV in N than in pts. - good correlation between % change in EF and % change in AoV
Maeda ⁴¹ (1989)	TME, CWD	21	34	- no differences between the Doppler response in N and pts. with single vessel disease with and without ischaemic ECG - lower \uparrow in AoV in pts. with multivessel disease or pts. with exercise-induced \uparrow in PAWP
Harrison ⁴² (1987)	TME, CWD, thallium perfusion scanning	28	74	- greater \uparrow in AoV and AoAcc in N than pts. with normal (25 pts.) or abnormal (49 pts.) thallium scans -pts. with abnormal scans had lower AoAcc than pts. with normal scans with the most pronounced difference seen in pts. with multivessel disease
\uparrow = increase, \downarrow = decrease. AoAcc = aortic acceleration, AoV = peak aortic velocity, CWD = continuous wave Doppler, EF = ejection fraction, N = normal subjects, PAWP = pulmonary artery wedge pressure, pts. = patients with CAD, PWD = pulsed wave Doppler, TME = treadmill exercise, TVI = systolic time velocity integral.				

Table IV. Studies evaluating the value of Doppler ejection parameters during pharmacologic stress testing for the evaluation patients with CAD.

Author	Technique	Subjects		Findings
		N	pts.	
Labovitz ⁴³ (1988)	DIP, CWD, Echo, thallium		94	- greater ↑ in EF, AoV and AoAcc in response to DIP in pts. with normal scans (41 pts.) than abnormal scans (53 pts.) - these differences were more pronounced in pts. with multivessel disease
Grayburn ⁴⁴ (1989)	DIP, CWD, thallium	10	23	-Doppler systolic indices are insensitive in detecting reversible perfusion defects or significant CAD
Agati ⁴⁵ (1990)	DIP, CWD, Echo, haemo- dynamics	13	29	- ↑ AoV and TVI in N but not in pts. - changes in Doppler indices are closely related to peak positive dp/dt, LV end-diastolic pressure, appearance of WMA, and coronary angiographic jeopardy score
Mazeika ⁴⁶ (1991)	DIP, PWD, Echo,	12	22	- no difference in the effect of DIP on AoV and AoAcc between N and pts. - ↓ AoV and AoAcc in pts. with severe ischaemia
Mazeika ⁷ (1992)	DOB, PWD, Echo	10	24	- ↑ AoV, AoAcc and TVI in N and pts. - Doppler indices responded bluntly to DOB in pts. with WMA in ≥3 segments
El-Said ⁸ (1993)	DOB, CWD, Echo	11	16	- DOB induced similar ↑ in AoV and AoAcc in N and pts. with 1-vessel disease both before and after PTCA. - AoV and AoAcc responded bluntly to DOB in 3 pts. with multivessel disease.
El-Said ⁹ (1994)	DOB, CWD, Echo	10	17	- DOB induced similar ↑ in AoV, AoAcc and TVI in N and pts. with 1-vessel disease
↑ = increase, ↓ = decrease. AoAcc = aortic acceleration, AoV = peak aortic velocity, CWD = continuous wave Doppler, DIP = dipyridamole stress test, DOB = dobutamine stress test, EF = ejection fraction, N = normal subjects, pts. = patients with CAD, PTCA = coronary angioplasty, PWD = pulsed wave Doppler, TVI = systolic time velocity integral, WMA = wall motion abnormalities.				

Table V. Influence of exercise-induced ischaemia on transmitral parameters of LV filling.

Author	Stress	Subjects		Findings
		N	pts.	
Kuecherer ⁵⁹ (1988)	UpBE	8	18	- during exercise, E/A \nless in N but \downarrow in pts.
Iwase ⁶⁰ (1989)	SupBE		27	- during exercise \uparrow E/A in pts. with PAWP ≥ 20 mm Hg at peak exercise but \downarrow in pts. with PAWP ≤ 10 mm Hg
Presti ⁶¹ (1991)	TME	20	20	- \uparrow E and A from rest to postexercise in N and pts.

\uparrow = increase, \downarrow = decrease, \nless = unchanged. A = atrial filling velocity, E = early filling velocity, E/A = early to atrial filling velocity ratio, N = normal subjects, PAWP = pulmonary artery wedge pressure, pts. = patients with CAD, SupBE = supine bicycle ergometer, TME = treadmill exercise, UpBE = upright bicycle ergometer.

Table VI. Influence of pacing-induced ischaemia on transmitral parameters of LV filling.

Author	Subjects		Findings
	N	pts.	
Iliceto ⁶² (1988)		17	- \downarrow E, \uparrow A and \downarrow E/A from rest to post pacing in pts. with pacing-induced ischaemia (ST depression) - no changes occurred in pts. without ischaemia
Gonzalez ⁶³ (1990)		17	- during pacing 7 pts. developed new or increasing mitral regurgitation with \uparrow E, \nless A and \uparrow E/A, - 10 pts. did not develop mitral regurgitation and showed no changes in Doppler indices during pacing
Furukawa ⁶⁴ (1990)	19	46	- no Doppler changes occurred in N, but there were \downarrow E, \uparrow A and \downarrow E/A 30-60 seconds postpacing in pts.

Abbreviations, see Table V.

Table VII. Influence of dipyridamole-induced ischaemia on transmitral parameters of LV filling.

Author	Subjects		Findings
	N	pts.	
Furukawa ⁶⁴ (1990)	19	33	- dipyridamole induced \uparrow in E and A in N and pts.
Grayburn ⁴⁴ (1989)	10	23	- Doppler diastolic indices are insensitive in detecting reversible perfusion defects or CAD
Tomimoto ⁶⁵ (1989)	8	73	- \downarrow E/A in pts. with dipyridamole-induced angina - no changes in N and pts. with negative test
Mazeika ⁴⁶ (1991)	12	20	- \uparrow E and A and \downarrow E/A in N and pts.
Abbreviations, see Table V.			

Table VIII. Influence of PTCA on transmitral parameters of LV filling.

Author	Time*	Number of pts.	Findings
Wind ⁶⁶ (1987)	within 1 day	34 (17 underwent PTCA)	- no differences in Doppler parameters before and after PTCA
Masuyama ⁶⁷ (1988)	2 & 9 days	50 with stable angina	- gradual \uparrow in E and E/A after PTCA
Castello ⁶⁸ (1990)	within 1 day	31 (15 stable and 16 unstable angina)	- \uparrow E/A and 1/3 filling fraction and \downarrow IRP and % atrial contribution to filling after PTCA
Snow ⁶⁹ (1990)	2 \pm 1 days	42	- after PTCA LV filling was improved (\downarrow IRP and DT)
El-Said ⁸ (1993)	within 3 days	17 with stable angina	- Doppler filling indices were comparable at rest, before and after PTCA - successful PTCA resulted in improvement in diastolic filling response to dobutamine stress
<p>* = timing of the Doppler examination after PTCA, \uparrow = increase, \downarrow = decrease. A = atrial filling velocity, DT = deceleration time, E = early filling velocity, E/A = early to atrial filling velocity ratio, IRP = isovolumic relaxation period, PTCA = coronary angioplasty</p>			

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SAMENVATTING EN CONCLUSIES

Sedert het gebruik van dobutamine bij stress echocardiografisch onderzoek zijn de volgende aspecten belicht: de uitvoerbaarheid, de veiligheid en de diagnostische nauwkeurigheid van de test. Tevens is getracht de gevoeligheid te verbeteren en de toepasbaarheid in verschillende klinische situaties te evalueren bij patiënten met coronarialijden. Dit proefschrift richt zich vooral op het uittesten van verschillende aanvullende methoden om de gevoeligheid van de dobutamine stress test te verhogen. Tevens is de bruikbaarheid van deze test onderzocht bij de beoordeling van patiënten die een PTCA ondergaan. Hiertoe werd(en): (a) het dobutamine stress protocol uitgebreid door toevoeging van atropine (hoofdstuk 3); (b) Doppler onderzoek toegevoegd aan de bestaande analyse van regionale wandbeweging ter evaluatie van de globale systolische en diastolische linker ventrikelfunctie (hoofdstuk 5 en 6); (c) de reproduceerbaarheid onderzocht van de beoordeling van wandbewegingsstoornissen en van de Doppler metingen betreffende de vullingsfase van de linker ventrikel (hoofdstuk 7 en 8); en (d) de veranderingen beoordeeld, voor en na PTCA, van het electrocardiogram, de regionale wandbewegingen en de Doppler metingen van de mitralis- en aortaflow gedurende de dobutamine stress test (hoofdstuk 4 en 5).

De in dit proefschrift beschreven resultaten bevestigen de superioriteit van de door dobutamine geïnduceerde wandbewegingsstoornissen als teken van myocard ischemie boven ECG veranderingen of angina pectoris. Toevoeging van atropine aan stress echocardiografisch onderzoek verhoogt de gevoeligheid van de test voor het opsporen van coronarialijden zonder verlies van specificiteit en zonder toename van bijwerkingen. Deze bevinding is met name van belang bij patiënten, die nog anti-angineuze medicatie gebruiken, in het bijzonder β -blockers, tijdens een dobutamine stress test.

Dobutamine-atropine stress echocardiografie blijkt eveneens van waarde voor het aantonen van de afname van induceerbare myocardi-schemie kort na PTCA. In het Thoraxcentrum wordt uitstekende reproduceerbaarheid verkregen van de dobutamine-atropine stress test. Hierdoor is de test een potentieel bruikbaar instrument voor het aantonen van progressie van coronarialijden. Bovendien kunnen de effecten van therapeutisch handelen bij deze patiënten hiermee worden geëvalueerd.

Het gebruik van Doppler metingen van de aorta flow snelheid gedurende de dobutamine stress test, is niet waardevol gebleken voor het herkennen van individuele patiënten met coronarialijden. Echter, de toevoeging van Doppler metingen van de linker ventrikelvulling ter plaatse van de mitraalklep, lijkt wel bruikbare informatie over het optreden van myocard ischemie te verschaffen. Dit is mogelijk een gevoeliger methode dan het vaststellen van regionale wandbewegingsstoornissen. Bovendien lijkt Doppler onderzoek van de linker ventrikelvulling voor en na therapeutische procedures bruikbaar in het voorspellen van het succes van die procedure. Echter, indien een dergelijk Doppler onderzoek van de linker ventrikelvulling in de praktijk wordt toegepast, dienen drempelwaarden (gebaseerd op een aantal slagen) te worden bepaald, ten einde een referentie te hebben om in het individuele geval significante veranderingen tussen uitgangswaarde en maximale belasting op te kunnen sporen.

Alhoewel de dobutamine stress test zich op een grote populariteit in de kliniek kan verheugen, is verder onderzoek nodig. Ten eerste is de interobserver variabiliteit, betreffende de interpretatie van de test tussen verschillende centra niet onderzocht. Dergelijke studies zouden de betrouwbaarheid van de test kunnen verhogen.

Ten tweede is er nog steeds een debat gaande omtrent de interpretatie van door dobutamine geïnduceerde verslechtering van reeds in rust bestaande wandbewegingsstoornissen. Het is de vraag of akinesie/ernstige hypokinesie, welke gedurende stress dyskinetisch wordt, beschouwd moeten worden als myocardischemie of als een mechanisch fenomeen. Dit is een belangrijk klinisch probleem, welke nader onderzoek verlangt.

Ten derde, eenvoudige en reproduceerbare methoden om linker ventrikel volumina of regionale wandverdikking te kwantificeren ontbreken. Kwantitatieve analyse zal in de toekomst eenvoudiger kunnen zijn en breder toepasbaar indien gebruik gemaakt wordt van recent ontwikkelde automatische contourdetectie, de beeldkwaliteit zoals verkregen met slokdarmechocardiografie en de technische ontwikkelingen op het gebied van driedimensionale reconstructie.

Ondanks de beperkingen van de Doppler methode dient dobutamine stress onderzoek zich niet te beperken tot het echocardiografisch beoordelen van wandbeweging, maar uitgebreid te worden met hemodynamische metingen van de systolische en diastolische linker ventrikel functie.

ACKNOWLEDGEMENTS

My deepest appreciation goes to *Prof. Jos Roelandt* who provided the unique opportunity to work at the Thoraxcenter. In his acceptance letter, he wrote to me " I am sure you will have a most interesting and productive scholarship period in Rotterdam ". After two and half years working at the Thoraxcenter, I realized that these words were absolutely true. It is true to say that this project would not have succeeded without the encouragement and the ability of *Prof. Roelandt* to see possibilities invisible to most. His creativity and determination to achieve the intended goal are well recognized and have been an example to those who have worked with him. I am very grateful for the hours he has spent in reviewing the articles of this thesis, for the continuous support, and for all the information on the Egyptian history and in particular those on Pharaonic Medicine.

I owe a particular debt to *Prof. MoKhtar Gomaa*, who's valuable advice and encouragement pointed me in the right direction and ensured that I continued in the field of cardiology. A most kind and generous individual. Amongst his many qualities was the ability to provide a valuable insight into the practicalities of clinical medicine. *Dr Gomaa* was a constant source of stimulation and support. Words are not sufficient to express my gratitude.

I would like to convey my appreciation to my co-promotor *Dr. Paolo Fioretti* and to *Dr. David Linker*, for their indispensable role in preparing this thesis. Their invaluable scientific criticism and ideas had a decisive influence which have enabled this work to become reality.

As someone with no experience in the sophisticated field of computer, I was greatly assisted by *Bas van der Borden*, whose patient assistance is reflected in many parts of this work.

Albert McNeill was of a great help and contribution in many of the studies presented in this thesis and I am very grateful to him and his wife for their sincere friendship. My "paranimf" *Wim Vletter* provided a great support and many valuable suggestions in the preparation of these manuscripts, thank you Wim. *Hans Rijsterborgh* and *Eric Boersma* contributed significantly in the statistics of the manuscripts. *Paolo Bellotti* and *Tamas Forster* were among those who contributed actively in the preparation of these studies. I wish to thank *Folkert ten Cate* and *Taams Meine Aldert* who taught me transoesophageal echocardiography. Special thanks goes to those who have provided help and support and whose friendship and company I have enjoyed. They include *Jan Hein*

Cornel, Don Poldermans, Marc van Daele, Carlo De Mario, Ian Thomson, Peter Widimsky, Alessandro Salustri, Fan Dong, David Waldstein, Rosi Arnese and Abdo El-Hendy.

There are many working in the Thoraxcentre who have provided help and support and to whom I am very grateful: M. Eichholtz, J. Tuin, All Members of the Computer Group, Ria Eldering-Gerritsen, Willeke Korpershoek, Dineke de Bruyn, Arita Orgers, Ad van Drunen and Marian, Janette and Mike.

I owe a great debt to all those working in the Echocardiography Laboratory and Department of Nuclear Medicine and thank them for their patience and help during the two and half years that I worked with them.

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