DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHY

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a method for preoperative cardiac risk stratification in
patients undergoing major vascular surgery

DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAFIE

een test om preoperatief het perioperatieve cardiale risico
te bepalen bij patienten die een uitgebreide vaatoperatie ondergaan

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 plaatsvinden
op woensdag 2 februari 1994 om 15.45 uur
door

Daniël Poldermans

geboren te Rotterdam

Promotiecommissie

Promotor : Prof. Dr H. van Urk

Co-promotor : Dr P.M. Fioretti

Overige leden : Prof. Dr A.J. Man in 't Veld
Prof. J.H.P. Wilson

Financial support for publication of this thesis was generously provided by: Glaxo, Novo Nordisk Farma, Pfizer, Duphar Nederland, Merck Sharp & Dome, Diasonics-Sonatron, Parke-Davis, Rhône-Poulenc Rorer, Sanofi-Winthrop, Zambon, ICI and Lilly.

To my parents
To Virginie and Laura

CONTENTS

CHAPTER 1

INTRODUCTION

Atherosclerosis is a systemic disease that may affect several blood vessels in different organs simultaneously. The spectrum of disease ranges from stroke to myocardial infarction, aortic aneurysms and peripheral vascular insufficiency. Patients suffering from one aspect of atherosclerotic disease will often have asymptomatic lesions elsewhere. Most patients seen with vascular disease by the internist or surgeon have a high prevalence of coronary artery disease, for example, 40-70% of patients undergoing major vascular surgery without clinically evident coronary artery disease will indeed have angiographically demonstrable coronary artery stenosis[1]. The coronary artery disease may be dormant due to lack of exercise but will undoubtedly have an impact on the management of patients. In patients undergoing vascular surgery coronary artery disease contributes to both perioperative and late death.

The number of patients with vascular disease and concomitant coronary artery disease is increasing as the prevalence of cardiovascular diseases increases with age, and the population of Europe is aging rapidly. The number of people over 60 years of age in Europe will probably increase with more than 92 million to 224 million in the year 2025[2].

Conventional testing in patients with vascular disease for coronary artery disease by exercise stress tests is often impossible due to noncardiac disease. Most patients are suffering from claudication or neurological disease.

In these patients dobutamine-atropine stress echocardiography may a new promising method to detect coronary artery disease[3-5]. This form of stress simulates physical exercise by a pharmacological agent while the patient is in a resting and supine position. Myocardial stress is induced by giving incremental intravenous doses of dobutamine which increase oxygen consumption by a positive inotropic and chronotropic effect on the heart[6]. The hallmarks of echocardiographically detected myocardial ischemia are: 1) reduced systolic wall thickening, and 2) transient wall motion abnormalities[7]. The stress test provides information of the left ventricular function at rest and the presence of myocardial ischemia during stress. The combined information of left ventricular dysfunction at rest and myocardial ischemia during stress provides information about the cardiac condition and prognostic information for late cardiac events[1].

In *chapter 2* the historical development of the dobutamine stress test will be discussed and the most widely used dobutamine stress protocol is compared with other pharmacological stress agents, like dipyridamole, adenosine and arbutamine for echocardiographic detection of coronary artery disease.

In *chapter 3* the safety and feasibility of the dobutamine-atropine stress test will be discussed. In the past, dobutamine was considered potential arrhythmogenic and safety may be questioned in patients referred for chest pain with a high likelihood of coronary artery disease. We studied the safety, side effects and feasibility in a large group of patients referred for chest pain.

In *chapter 4* the influence of beta blocker medication on stress test results will be discussed. The action of dobutamine is partially antagonized by beta blockers which reduce the chronotropic effect of dobutamine. Stopping of beta blockers may be impractical in patients with chest pain. To overcome the action of beta blockers we added atropine and studied the efficacy and safety in a cross-over study.

In *chapter 5* the heart response to dobutamine in elderly patients will be discussed. It is generally accepted that the ß-adrenergic receptor becomes less sensitive in senescent patients. This is based on studies with animals and humans which show a decreased heart rate response to isoproterenol infusions. This might have practical implications on the stress test protocol in the elderly. We studied the effect of dobutamine, a relative selective $ß_1$-adrenoceptor agonist with weak α and $ß_2$-adrenoceptor stimulant activity on heart rate response in elderly.

In the second part the clinical applications of stress echocardiography will be discussed.

In *chapters 6 and 7* the value of preoperative cardiac risk stratification in patients scheduled for elective major vascular surgery will be discussed. These patients have a high incidence of coronary artery disease[1] which has an impact on perioperative and late mortality. The conventional tests for coronary artery disease, as exercise electrocardiography is often impossible due to lack of

physical exercise for noncardiac reasons. Apart from information on the present cardiac condition the dobutamine-atropine stress test may provide prognostic information for late cardiac events. This information might be useful to select before operation patients with a high cardiac risk.

In *chapter 8* the application of the stress test in the very elderly (≥70 years) will be discussed for preoperative cardiac risk stratification and prognostic value for late cardiac events. In these patients adequate physical exercise is often impossible due to claudication, neurological or orthopaedic diseases. A stress test in resting, supine position independent of physical exercise might be useful. We studied the safety and prognostic value in elderly patients.

In *chapter 9* the prognostic value for late cardiac events in patients referred for chest pain complaints will be discussed. Patients were studied and followed for 17 ± 5 months. Test results, in contrast to most other studies were not used for clinical management. Study end-points were fatal and non-fatal infarction or coronary revascularisation. We used coronary revascularisation instead of unstable angina pectoris to perform a comparison with other stress tests[8].

In *chapter 10* a review and conclusions are given of the current concepts about the value of dobutamine-atropine stress echocardiography.

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CHAPTER 2

DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHY FOR DETECTION OF MYOCARDIAL ISCHEMIA: PHYSIOLOGY, CLINICAL USE AND PROGNOSTIC VALUE[1]

Don Poldermans*, MD and Paolo M. Fioretti, MD

From the Thoraxcenter and Department of Surgery*, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, The Netherlands.

Introduction

The clinical use of stress echocardiography has increased over the last five years[1-5]. The test has the potential to assess the site and the extent of myocardial wall motion abnormalities at rest and during stress. Reduced wall thickening and transient wall motion abnormalities are the hallmark of myocardial ischemia[2]. Ischemia represents an imbalance between oxygen supply and demand. Myocardial oxygen consumption is determined by heart rate, myocardial wall stress and contractility. Coronary blood flow reserve is the limiting factor for oxygen supply during stress as energy is provided by aerobic metabolism with limited anaerobic reserve. Coronary artery disease detected by stress is a functional abnormality, compared to the anatomical evaluation by coronary angiography.

Myocardial stress can be induced by 1) exercise; 2) cold pressure; 3) sustained handgrip; 4) mental stress; 5) pharmacological agents and 6) hyperventilation.

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[1] Cardioscopies, accepted for publication

Pharmacological agents used are ergonovine, adenosine, dipyridamole, arbutamine and dobutamine. Ergonovine can induce ischemia by coronary vasospasm. Dobutamine and arbutamine increase myocardial oxygen demand by a positive chronotropic and inotropic effect on the heart[6,7] and can be regarded as some pharmacological tests simulating exercise. Adenosine and dipyridamole increase adenosine concentration, dipyridamole by inhibition of the cellular re uptake of endogenously produced adenosine, and induce coronary vasodilatation and heart rate increase. Coronary vasodilatation will paradoxical lead to ischemia because of a flow redistribution at the expense of stenotic arteries and subsequent post stenotic ischemia (steal effect).

Besides detecting myocardial ischemia dobutamine stress echocardiography is presently also used for studying myocardial viability. Viable myocardium will show an improved movement during low dose of dobutamine.

Noninvasive testing in patients with proven or suspected coronary artery disease will become more important in the future as the proportion of people over 60 years of age (with an increasing incidence of cardiovascular disease) in Europe will grow to over 60% by 2025[8]. This review will discuss the background, clinical use and prognostic information of stress echocardiography for detecting myocardial ischemia, with particular focus on dobutamine stress testing.

Background

Coronary artery stenosis can be unmasked by stress induced myocardial ischemia due to an increase in oxygen demand (exercise, mental stress, cold pressure test, sustained handgrip, arbutamine and dobutamine) or limited supply (steal phenomenon induced by vasodilatation by adenosine or dipyridamole). Coronary vasospasm, on top of any degree of coronary artery disease can be induced by ergonovine or hyperventilation.

Exercise stress: exercise was the first reported and used form of stress echocardiography. Exercise increases myocardial oxygen demand by an increase in heart rate and blood pressure and is still considered as the most physiological stress. In patients with significant coronary artery disease blood flow cannot increase sufficiently to meet demand and will lead to ischemia. Exercise stress echocardiography has also in our experience a better diagnostic accuracy for diagnosing the presence and extent of coronary artery disease than exercise electrocardiography[9,10]. Exercise can be done on a treadmill or bicycle, the later in upright or supine position. Treadmill exercise has the disadvantage of no reliable recordings during stress because of hyperventilation and only after peak exercise a complete echo recording can be performed. This excludes close echocardiographic monitoring during stress and early detection of ischemia.

Also there can be a delay in post-exercise monitoring as especially elderly people are not able to transfer rapidly in the supine position. It is considered that transfer time and echo acquisition should be as short as possible. This might influence the detection of mild coronary artery disease which causes short lasting abnormalities.

Bicycle exercise stress echocardiography can be monitored during stress. Compared to treadmill exercise it induces greater heart rate and blood pressure product at the same workload.

Exercise stress echocardiography detects significant coronary artery disease (diameter stenosis >50%) with a sensitivity range of 58-86% and a specificity range of 64-100%[9-14]. The sensitivity for detection of single vessel disease is less compared to multi vessel disease. A new promising method is the supine bicycle stress test developed by Hecht et al.[14]. Performing the echo at peak stress these authors found an extremely high diagnostic accuracy. However such data have to be reproduced by other groups before they can be considered conclusive. The accuracy of the test can be influenced by 1) experience of investigators and image quality. 2) presence of a previous myocardial infarction. 3) digital line loop system is mandatory, allowing side by side comparison of the different views at rest and post exercise, avoiding the effects of hyperventilation which makes interpretation of images more difficult. 4) the ability to perform physical exercise on a bicycle or treadmill as a large number of patients referred for stress testing are unable to perform adequate exercise (30%).

False negative results can be explained by: sub-optimal exercise, delay in recording after peak exercise, concurrent antianginal medication use and poor image quality. The diagnostic accuracy for coronary artery disease of exercise echocardiography and ^{201}Tl single photon emission computed tomography is comparable[9,10], the method of choice will greatly depend on the institutional experience[15].

Ischemia induced by coronary vasospasm is a transient reduction in luminal diameter superimposed on any degree of coronary artery stenosis[16]. Vasospasm can be induced by ergonovine, a nonspecific vasoconstrictor or by hyperventilation. Hyperventilation induces coronary spasm by systemic alkalosis

Pharmacological stress is attractive as many patients are unable to perform adequate physical exercise because of non-cardiac reasons. Elderly patients often have neurological, pulmonary, orthopaedic or vascular diseases which limit exercise capacity. The following pharmacological stress inducing agents will be discussed: 1) dobutamine in combination with atropine, 2) arbutamine, 3) adenosine and 4) dipyridamole.

Dobutamine is a sympathomimetic amine which stimulates β_1,β_2 and α_1 receptors. Originally used for its positive inotropic and chronotropic effect in cardiac failure[6]. The inotropic effect is mediated by α_1 and β_1 receptor stimulation, usually at low dose (10-20 µg/kg/minute) while β_1 stimulation is responsible for the chronotropic effect at higher doses (>20 µg/kg/minute). In the peripheral vasculature the β_2 mediated vasodilatation is almost balanced by the α_1 mediated vasoconstriction. Dobutamine causes an increase in cardiac output, due to an increase in stroke volume and a decrease in systemic vascular resistance because of a secondary reflex withdrawal of sympathetic tone. Consequently systemic blood pressure usually remains unaffected during dobutamine infusion.
Elderly patients (age >70 years) were thought to be less responsive to adrenergic stimulation due to a decreased receptor sensitivity[17]. This would imply higher doses of dobutamine in order to reach test end-point. This was not according to our results. The heart rate of elderly patients responded at least as good as "younger" patients.
Low dose dobutamine has a positive inotropic effect due to β_1 receptor stimulation. This may improve the function of hypokinetic myocardium at rest which may return to normal movement (hibernating myocardium).

The increase of myocardial oxygen consumption during dobutamine infusion, which closely resembles physical exercise[18], is more related to its chronotropic[19] then inotropic response. Besides increase in myocardial oxygen demand dobutamine also induces a maldistribution of coronary flow between endocardium and epicardium due to coronary vasodilatation which may potentiate the ischemic effect[20]. Atropine was combined with dobutamine in those patients who failed to reach test end-point (target heart rate or signs or symptoms of ischemia) with maximal dobutamine dose alone. Starting dose was 0.25 mg i.v. up to a maximum of 1.0 mg. The vagolytic action is responsible for the "boost" of heart rate.

Arbutamine: is a new developed catecholamine with beta agonist activity. Arbutamine increases heart rate, systolic blood pressure and myocardial contractility. The first study with arbutamine for stress induction show that it is effective and safe, although the number of patients studied is still limited[7].

Dipyridamole exerts its effect by increasing adenosine concentration, by reduced re-uptake of endogenously produced adenosine. It has also a mild chronotropic effect. Adenosine is a strong vasodilatator, the difference between adenosine administration and dipyridamole is the duration of action, half-life time of adenosine is seconds compared to 6 hours of dipyridamole. The vasodilatation can paradoxical induce ischemia due to coronary steal[21]. In vertical steal (subepicardial vs subendocardial) a combination of a stenotic subepicardial artery with vasodilatation is mandatory, with a concomitant fall in post-stenotic

pressure and collapse of the subendocardium vessels as extra vascular pressure is greatest there. In horizontal steal (normal vs stenosed arteries) after vasodilatation perfusion pressure decreases because of a reduced resistance (better run off) at the cost of collateral flow towards post-stenotic areas. Picano et al.[21] described this appropriately as the "reversed Robin Hood" effect, they steal from the poor (myocardium at risk) and give to the rich (myocardium well nourished in resting conditions).

The comparison of dobutamine and dipyridamole as pharmacological stress agents to perform stress echocardiography: Echocardiography allow diagnosis of ischemia by detecting new wall motion abnormalities during stress. Dobutamine is an "exercise stimulator" and is more effective in inducing new wall motion abnormalities then dipyridamole. This can be explained by the different mechanisms by which dobutamine and dipyridamole influence myocardial oxygen demand and supply. Dobutamine increases myocardial oxygen demand by augmentation of heart rate and contractility. In patients with significant coronary artery stenosis oxygen demand may exceed oxygen supply, leading to ischemia which results in abnormal wall motion and decrease of myocardial function. Dipyridamole results in a flow heterogeneity with reduction of flow in regions supplied by a stenotic artery. In patients with a moderate reduction of coronary flow no significant ischemia will occur, which explains the reduced sensitivity of echocardiography in detecting moderate coronary artery disease. This is supported by both animal studies[22] and later patient studies by Marwick et al.[23,24] Dipyridamole induces a maldistribution of flow and will be the pharmacological agent of choice in perfusion imaging like thallium scintigraphy.

Echocardiography: Echocardiographic detected reduced wall thickening and wall motion abnormality are early markers of ischemia. The signs and symptoms follow a "cascade" of events, starting with perfusion heterogeneity between subepicardial and subendocardial regions, metabolic changes, disturbance of diastolic ventricular relaxation, regional dyssynergy. Electrocardiographic changes and chest pain occur rather late and are unspecific as resting electrocardiographic changes may preclude ST segment changes for analysis of ischemia and patients, especially diabetic, may have silent ischemia. Normal myocardium shows an increase of movement and thickening during stress. The hall mark of ischemia is reduced wall thickening and transient, regional wall motion abnormalities, divided in three degrees: hypokinesis (reduction of systolic movement), akinesis (absence of systolic movement), and dyskinesis (paradoxical systolic movement).

Interpretation: In areas with a normal resting echocardiography some investigators use an absence of wall thickening as an early sign of ischemia,

which is more difficult to assess and may be classified as "relative" hypokinesia[23], while other investigators use the occurrence of combined wall motion abnormalities and reduced thickening as a more definite marker. In practice wall motion and thickening abnormalities occur simultaneous, with few exceptions as seen after cardiac surgery. Dobutamine has advantage of hyperkinesis of normal myocardium. This difference between normal and ischemic areas becomes greater which helps interpretation. This is not the case with dipyridamole. Wall motion score is determined at rest and during stress using a semi-quantitative assessment of the left ventricular wall which was divided into 14 segments and each was scored using a 4 point scale: 1 = normal, 2 = hypokinetic (decrease of movement and systolic thickening), 3 = akinetic (absence of movement and systolic thickening), and 4 = dyskinetic (paradoxical outward movement and possible systolic movement)[25]. The American Society of Echocardiography proposed a 16-segment model which is similar to the model already described with two additional segments, basal and medium part of the posterior wall. An increase in score between rest and stress is not diagnostic for ischemia as some parts may improve during dobutamine (hibernating myocardium) while other parts may deteriorate resulting in a balanced score.

Resting abnormalities make the diagnosis of a new wall motion abnormality difficult and this is further increased when the heart becomes more dilated. We consider any deterioration of wall motion as abnormal, an area which is hypokinetic at rest may become a or dyskinetic during stress and is considered as a positive test.

The diagnostic accuracy will depend greatly on the "quality" of the investigator which will improve during training, Picano et al.[26] stated that 100 stress echocardiographic studies are more than adequate for this.

Dobutamine infusion protocol: we developed a "standard" dobutamine stress protocol which is now increasingly being used by others[27].

This protocol allows patients to continue their anti-anginal medication, especially beta blockers, which was thought to inhibit the action of dobutamine by the addition of atropine in patients who did not reach target heart rate during dobutamine infusion alone.

Patients underwent a resting two-dimensional precordial echocardiographic examination. Standard apical and parasternal views were recorded on video tape and a 12-lead ECG was recorded. Dobutamine was then administrated intravenously by infusion pump, starting at 10 μg/kg/minute for 3 minutes, increasing by 10 μg/kg/minute every 3 minutes to a maximum of 40 μg/kg/minute (stage 4), and continued for 6 minutes. In patients not achieving 85% of their age predicted maximal heart rate who had no symptoms or signs of ischemia, atropine (starting with 0.25 mg increasing to a maximum of 1 mg) was given intravenously at the end of stage 4, while dobutamine was continued.

Throughout dobutamine infusion the ECG was continuously monitored, the 12-lead ECG was recorded each minute and the blood pressure was measured by sphygmomanometry or automatic device every 3 minutes. The two-dimensional echocardiogram was continuously monitored on quad screen display for side by side examination of the rest and stress images and recorded on video tape during the final minute of each stage. Metoprolol was available and used (1 to 5 mg intravenously) to reverse the effect of dobutamine or dobutamine-atropine combination if these did not revert spontaneously and quickly. Atropine was used if bradycardia occurred. Off-line assessment of echographic images was usually performed by two investigators. In case of disagreement, a third investigator viewed the images and a majority decision was achieved.

The starting dose of dobutamine, maximum dose and addition of atropine in cases were patients do not reach test-end point varies with different investigators. In case of a lower dobutamine dose, usually anti-anginal medication is stopped for 4 half-lives times before the study and the interval between dose adjustments is longer, 8 versus 3 minutes (table 1).

Table 1 Comparison of different dobutamine stress protocols

	year	start	peak	interval
Berthe[31]	1986	5	40	3
Mannering[32]	1988	5	20	6-8
Mazeika[1]	1991	5	20	8
Previtali[34]	1991	5	40	5
Cohen[33]	1991	2.5	40	3
Sawada[35]	1991	2.5	30	3
McNeill[27]	1992	10	40	3
Segar[37]	1992	5	30	3
Marcovitz[41]	1992	5	30	3
Lalka[40]	1992	2.5	50	3
Marwick[23]	1993	5	40	3

Start = starting dose dobutamine (μg/kg/minute); peak = maximum dose dobutamine (μg/kg/minute); interval = time (minutes) between dose adjustments; A = atropine addition.

Atropine addition: we introduced atropine addition on top of maximum dose dobutamine in patient who did not reach target heart rate and had no signs or markers of ischemia, mostly patients on beta blocker medication[28]. The starting dose was 0.25 mg i.v. which was repeated if necessary to 1 mg i.v. In a cross-over study of 26 patients, examined on and off beta blocker medication the addition of atropine increased the detection of new wall motion abnormalities. During dobutamine stress new wall motion abnormalities occurred on beta

blocker medication in 3/26, increasing to 15/26 after atropine addition. These same patients without beta blocker medication showed new wall motion abnormalities in 12/26 patients during dobutamine alone, increasing only to 14/26 if atropine was added. The addition of atropine resulted in a substantial increase of sensitivity without influence on specificity of the test without extra side effects.

Test end-point of dobutamine-atropine stress test: test end-point of stress test is target heart rate (male: 220-age[years] X 85%; female: 200-age[years] X 85%). Interruption criteria for the test are: horizontal or down sloping ST depression >2mm at 80 ms after the J point, ST elevation, significant chest pain, reduction in systolic blood pressure >40 mmHg from that at rest, hypertension (systolic blood pressure ≥220 mmHg), decrease of heart rate ≥10 beats per minute from that at rest or any other side effect regarded as being due to dobutamine. A new wall motion abnormality was considered as an interruption criteria in absence of side effects or other markers of ischemia only if it was severe and extensive.

We have previously shown excellent inter and intra-observer reproducibility of interpretation of stress echocardiography, of 91% and 92% respectively[9]. In addition the reproducibility of wall motion abnormalities was 100% in 23 patients who underwent two serial studies on different days[29].

In a small percentage we were unable to get adequate echo images, in 650 examinations this occurred in 2 patients, both had severe pulmonary disease. Target heart rate was reached in 90%, in 10% the test was stopped because of side effects. Other groups find less favourable results, a study of Mertes et al.[30] is shown in table 2. We think in the future as experience with dobutamine stress echo increases investigators will be more "aggressive" in reaching target heart rate as test end-point.

Side effects: Side effects related to dobutamine-atropine stress test are mostly angina pectoris, electrocardiographic changes, cardiac arrhythmias and hypotension. Other less common side effects are chills, hypertension, headache and anxiety.
Cardiac arrhythmias occur during stress test in 11% of the cases, most of them of minor importance (table 3[1,4,27,30-42]).

The addition of atropine, used in the studies of McNeill[27], Mertes[30], Previtali[34] and Poldermans[42] induced no extra cardiac arrhythmias. Cardiac arrhythmias caused an interruption of the stress test in only 0.5-2.1%. In our study we found a correlation between a history of a previous myocardial infarction (odds ratio 9.9, 95% C.I. 2.0-45), diffuse rest wall motion abnormalities (wall motion score index ≥1.12) (odds ratio 2.9, 95% C.I. 1.1-7.6) and cardiac arrhythmias, but not with atropine addition. There have been no reports of cardiac death in the

literature. Treatment of arrhythmias usually consists of stopping dobutamine infusion and if they do not revert quickly, the antidote beta blockers is given i.v.

Table 2 The interruption criteria in a study of 650 patients of our centre and of a study of Mertes et al.[30]

	No. 650*	No. 1118#
indication for stopping		
target heart rate	90 %	52 %
maximum dose	-	23 %
severe chest pain	4.6%	12.7%
ST segment changes	1.4%	1.1%
arrhythmias	1.9%	2.1%
new wall motion abnormalities	0.2%	-
noncardiac side effects	0.9%	3.2%
severe hypotension	0.6%	3.2%
hypertension	0.2%	0.9%

Arrhythmias = *(paroxysmal atrial fibrillation, sustained ventricular tachycardia = ≥10 beats; non sustained ventricular tachycardia = less then 10 beats and ventricular fibrillation), #(not specified); Hypotension = *systolic blood pressure decrease of >40 mmHg to baseline, #systolic blood pressure decrease ranged from 16 to 84 mmHg compared to baseline; hypertension = *systolic blood pressure ≥220 mmHg, #systolic blood pressure ≥250 mmHg; noncardiac side effects = *(chills), #(nausea, anxiety, headache, tremor and urgency)

One patient with ventricular fibrillation is reported. This was a 50 year old man with known symptomatic ventricular arrhythmias, previous myocardial infarctions and a markedly reduced left ventricular function, who was scheduled for major vascular surgery. Coronary angiography showed a two-vessel disease with a left ventricular ejection fraction of 15%. During dobutamine infusion, (40 μg/kg/minute) this patient developed ventricular fibrillation and was successfully resuscitated without evidence of a new myocardial infarction based on echocardiography, electrocardiography and cardiac isoenzymes. This patient was operated on 1 week later without complications and is doing well 8 months later.

Table 3 Review of dobutamine stress test and cardiac arrhythmias

	year	No.	No. side effects	side effects
Berthe[31]	1986	30	0/30	
Mannering[32]	1988	50	1/20	1 Non sustained VT
Mazeika[1]	1991	46	0/46	
Cohen[33]	1991	74	20/40	1 Atrial fibrillation 5 Non sustained VT 14 Ventricular arrhythmias
Previtali[34]	1991	35	11/35	11 Ventricular arrhythmias
Sawada[35]	1991	202	16/202	1 Atrial fibrillation 15 Ventricular arrhythmias
Salustri[4]	1992	52	0/52	
McNeill[27]	1992	80	3/80	3 Non sustained VT
Mazeika[36]	1992	50	15/50	1 SVT 14 Ventricular arrhythmias
Segar[37]	1992	85	0/85	
Mertes[30]	1993	1118	266/1118	40 VT Non sustained 7 Atrialfibrillation 1 Atrial flutter 38 SVT 180 Ventricular arrhythmias
Pingitore[38]	1992	284	16/284	1 SVT 15 Ventricular arrhythmias
Pellikka[39]	1992	24	0/24	
Lalka[40]	1992	60	2/60	1 VT 2 SVT
Marcovitz[41]	1992	568	5/568	3 Atrial fibrillation 2 SVT
Poldermans[42]	1993	650	24/650	1 VF 3 VT 12 Non sustained VT 8 Atrial fibrillation
		3408	379 (11%)	

VF = ventricular fibrillation; VT = ventricular tachycardia; SVT = supra ventricular tachycardia.

Paradoxical hypotension during dobutamine infusion may occur[43-46]. The definition of hypotension varies which may influence its occurrence. We and others[23] define a drop in systolic blood pressure of >20 mmHg as hypotension, while others use >15 mmHg[35] or >30 mmHg[37] compared to base line value. The frequency varies between 11 and 20%. In contrast to exercise stress testing, were hypotension is related with acute pump failure, no correlation was found between new wall motion abnormalities and hypotension during the test. Proposed mechanisms for hypotension are a mild vasodilator effect of dobutamine at higher doses, dynamic left ventricular outflow obstruction or a consequence of vigorous contraction of the left ventricle with parasympatic activation and sympathomimetic withdraw and subsequent bradycardia and

hypotension[44]. Marcovitz et al.[43] presented data which suggest the presence of a subgroup of patients with a more gradual decrease of blood pressure associated with more severe coronary artery disease in contrast to patients with a more sudden decrease of blood pressure were no correlation with ischemia was found.

In our protocol a drop in systolic blood pressure >20 mmHg compared to rest value is defined as hypotension. In few patients this causes discomfort and is usually well accepted, very few patients have a more abundant and symptomatic blood pressure fall, >40 mmHg systolic blood pressure reduction which necessitates interruption of the test. There was no correlation with severe hypotension and myocardial ischemia in our study.

In conclusion: we have only few contra-indications for the test, as we think the safety is "strengthen" by the continuous echocardiographic monitoring. Patients with severe hypertension and cardiac arrhythmias must be excluded from the test.

Dobutamine-atropine stress echocardiography: clinical use and prognostic value

The dobutamine stress test is widely used for the diagnosis of coronary artery disease[1-4], risk stratification after acute myocardial infarction[31] and stratification in patients scheduled for elective major vascular surgery[40,42,47,48].

The diagnostic value for significant coronary artery disease (diameter stenosis >50%) has a sensitivity which ranges from 54 to 96% and specificity from 60 to 100% (table 4).

Table 4 Review of dobutamine stress echocardiography and detection of significant coronary artery disease (diameter stenosis >50%)

	year	No	Atropine	Sens %	Spec %
Berthe[31]	1988	30	No	85	88
Cohen[33]	1991	70	No	86	95
Mazeika[36]	1992	50	No	78	93
Sawada[35]	1991	103	No	89	85
Previtali[34]	1991	35	No	68	100
Segar[37]	1992	85	No	95	82
Marcovitz[41]	1992	141	No	96	66
McNeill[27]	1992	80	Yes	70	88
Salustri[4]	1992	52	No	54	80
Martin[49]	1992	40	No	76	60

The test has a high negative predictive value which selects patients with limited coronary artery disease. Important with interpretation remains the difference

between anatomical abnormalities, diagnosed by angiography and functional abnormalities found by stress echocardiography and the number of coronary arteries affected. In patients with one vessel disease sensitivity is less compared to multivessel disease[31,32-37,41]. Test results are also influenced by the stress protocol itself as patient with concomitant beta blocker medication benefit from atropine addition[27,28]. This can explain differences between investigators. As with all "new" investigations a referral bias can be introduced. Patients with a positive test will be more likely investigated by coronary angiography, thereby creating an enhanced sensitivity. The "false" negatives can be only evaluated by a follow-up study of several years.

Comparison dobutamine with dipyridamole and adenosine. Three studies have subsequent investigated the same patients with different stress protocols for detection of coronary artery disease (table 5). Previtali et al.[34] compared dipyridamole (high dose 0.84 mg/kg) with dobutamine (40 µg/kg/minute) in 35 patients. In this group the overall sensitivity for dobutamine was 68%, increasing to 92% for single vessel disease. Dipyridamole showed the same overall sensitivity, but only 31% if only single vessel disease was included. The specificity for both protocols was the same, 100%. Martin et al.[49] studied 25 patients with a sensitivity of dobutamine of 76% compared to dipyridamole of 56%. The specificity of dobutamine was 60% compared to dipyridamole of 93%. Marwick et al.[23] examined the difference between dobutamine and adenosine in 97 patients. The overall sensitivity of dobutamine was 84%, compared to 56% for adenosine. If only single vessel disease was included the sensitivity of dobutamine vs adenosine was 81% vs 50%. The specificity of dobutamine and adenosine was 82% respectively 92%, this difference was not significant. Salustri et al.[50] studied 46 patients in which 18 had significant coronary artery disease. Both dobutamine and dipyridamole showed similar sensitivity and specificity for detection of coronary artery disease.

The safety profile of dipyridamole is excellent as shown in a large study by Picano et al.[51], as previous mentioned the first results for dobutamine stress look also promising.

In conclusion dobutamine stress is probably more sensitive for detecting coronary artery disease compared to dipyridamole and adenosine, with the exception of the study of Salustri et al.[50] who found similar results.

Preoperative cardiac risk stratification: Cardiac risk stratification for patients scheduled for major noncardiac vascular surgery is one of the most promising applications of dobutamine stress echocardiography[40,42,47,48,62].

Perioperative cardiac complications are cardiac death, myocardial infarction, unstable angina pectoris and congestive heart failure. The incidence of perioperative events ranges from 1-15% in patients undergoing vascular surgery, with a mortality range from 5-10%[52]. Cardiac complications are common because of the high incidence of coronary artery disease[53,54] and surgical stress

in these patients. Numerous methods have been used to select high risk patients before operation[55-58]. After identification patients can be scheduled for a less extensive surgery, a cardiac intervention or will be given additional care such as a prolonged stay at the IC, perioperative ß-blockers and antithrombotic therapy.

Most patients are not able to perform adequate physical exercise, because of age and noncardiac diseases as peripheral vascular disease or stroke. Coronary artery disease is frequent in these patients and cardiac events are a leading cause of perioperative morbidity and mortality and long-term survival[52,53,60]. Numerous methods are developed to select preoperative patients with high cardiac risk[55-61]. Selection criteria based on clinical data are often invalid because of a lack of exercise which conceals coronary disease[55]. At the moment the most widely used method is a combination of clinical scoring and thallium scintigraphy[56].

Table 5 Review of different pharmacological stress agents and diagnosis of significant coronary artery disease (diameter stenosis >50%)

	year	No	drug	Sens %	Spec %	+ PV %	- PV %
Martin[49]	1993	40	adenosine	40	93	91	48
Marwick[23]	1993	97	adenosine	58	87	87	57
Previtali[34]	1991	35	dipyridamole	57	100	100	100
Martin[49]	1993	40	dipyridamole	50	56	42	78
Salustri[50]	1992	46	dipyridamole	82	89	90	44
Salustri[50]	1992	46	dobutamine	79	78	80	54
Previtali[34]	1991	35	dobutamine	68	100	100	38
Marwick[23]	1993	97	dobutamine	85	82	88	78
Martin[49]	1993	40	dobutamine	50	76	45	85

Sens = sensitivity; spec = specificity; PV = predictive value.

Thallium scintigraphy was long considered as the method of choice combined with dipyridamole[56-58]. The sensitivity, specificity for predicting perioperative cardiac events ranged from 83-100% and 62-80%. A review of 1404 patients from the literature showed a sensitivity of 90% and a specificity of 64% for perioperative cardiac death or myocardial infarction. These promising results were questioned in a article by Mangano et al.[59] who found a lower sensitivity of 46% with a negative predictive value of only 82%. The study by Mangano was well documented and test results were hidden from the attending physicians, but the incidence of "hard cardiac complications", cardiac death and infarction was low.

Pharmacological stress echocardiography is a promising new tool. Drugs that have been used are dipyridamole and dobutamine. As stated earlier

dipyridamole causes a coronary vasodilatation and induces ischemia by coronary steal. This makes the technique less sensitive for echocardiographic detected mild coronary disease. Dobutamine induces myocardial ischemia by an increased demand due to a positive chronotropic and inotropic effect. This test simulates physical exercise closely and has a great sensitivity for detecting even mild coronary artery disease. Perioperative cardiac complications are more related to severe coronary artery disease. This might explain the excellent results of Tischler et al.[61] with high positive and negative predictive value 78%-99%. However these data have to be reproduced by other groups before they can be considered conclusive.

Dobutamine, even combined with atropine has a less positive predictive value. A review of studies published so far show a positive predictive value range of 21%-32% and negative predictive value of 95-100% (table 6). These studies have to be expanded with larger number of patients, but look promising combing a relatively safe test with high negative predictive value.

Table 6 Review of value of new wall motion abnormalities detected by stress echocardiography for preoperative risk stratification of perioperative cardiac events in patients scheduled for major vascular surgery

	Stress	No	Se	Sp	+ PV	- PV	Event
Tischler[61]	Dipy	109	88	98	78	99	CD,MI, UAP,CHF
Lane[62]	Dobu	57	100	56	21	100	CD,MI, UAP
Poldermans[42]	Dobu	187	100	77	32	100	CD,MI, UAP,CHF
Lalka[40]	Dobu	60	85	44	29	95	CD,MI, UAP
Eichelberger[48]	Dobu	70	100	66	19	100	MI,UAP

Dipy = dipyridamole; Dobu = dobutamine; Se = sensitivity %; Sp = specificity %; + PV = positive predictive value %; - PV = negative predictive value %; CD = cardiac death; MI = myocardial infarction; UAP = unstable angina pectoris; CHF = congestive heart failure.

A proposed work-up for preoperative cardiac risk stratification in patients scheduled for major vascular surgery would be: 1) stress echocardiography, patients with a negative test can be sent for surgery without extra investigations. 2) patients with a positive test should receive extra treatment in addition to clinical management. The relatively low perioperative cardiac mortality in later studies, ranging from 1.6% to 3.3% do not warrant routine preoperative coronary revascularisation with a waiting list and mortality rate of its own.

The proposed treatment would be: 1) perioperative ß-blockers with a short half-life time, like esmolol with a half-life time of 9 minutes combined with antithrombotic treatment; 2) perioperative monitoring for ischemia with continuous electrocardiagraphy trans oesophageal echocardiography and a prolonged stay at the IC as most of the cardiac events occur in the first 7 days after surgery; 3) postoperative patients should be carefully monitored for cardiac complaints as their exercise capacity increases.

Prognostic value: Patients outcome, cardiac death, ischemia or infarction, provides the most reliable prognostic information of a cardiac stress test. Coronary angiography provides excellent prognostic information[53], noninvasive testing as exercise electrocardiography[63,64], ambulatory Holter tape with ST segment monitoring[65] and thallium scintigraphy are alternatives[66,67].

Stress echocardiography is a relatively new tool for prognostic risk stratification. Exercise[68], dipyridamole[69] and recently dobutamine[70,71] stress echocardiography are used as a prognostic test. Sawada et al.[68] has shown with exercise echocardiography a good prognosis of patients with a negative test, 148 patients were followed for 28 ± 9 months, 6 cardiac events occurred all in patients who performed submaximal exercise. Drawbacks of this study is the low incidence of coronary artery disease (39%) and percentage of males (52%) included. Dipyridamole stress echocardiography was studied by Picano et al.[69]. In this large study, 539 patients, 118 events occurred. The sensitivity/specificity of a positive dipyridamole stress test was 88%/57%% with a positive/negative predictive value of 36%/94%. A positive stress test was the best predictor of cardiac events followed by an abnormal coronary angiography. The prognostic value of dobutamine stress echocardiography was examined in 2 studies[70,71] and recently we have finished a study (table 7).

All studies a significant relation between new wall motion abnormalities and late cardiac events. In our study we separated cardiac death, cardiac death or myocardial infarction, unstable angina pectoris and all cardiac events. By multivariate analysis there was a significant correlation between 1) cardiac death and rest wall motion abnormalities (rest wall motion score index ≥1.12) (odds ratio 3.9, 1.1-14.2), 2) cardiac death or myocardial infarction and a history of a previous infarction (odds ratio 5.2, 1.6-15) and ST segment changes during stress (odds ratio 2.4, 1.1-5.4), 3) unstable angina pectoris and new wall motion abnormalities (odds ratio 2.3, 1.3-4.1). If these events were combined only new wall motion abnormalities were predictive for late events (odds ratio 2.3, 1.4-3.7). This is in accordance with previous findings indicating a relation between poor left ventricular function and cardiac death and inducible myocardial ischemia with late cardiac events[69].

All these studies show a low positive predictive value for late cardiac events. Explanation for this can be the relatively low cardiac event rate, at first as experience is limited less severe cardiac disease is examined, and the disease

itself may be difficult to predict for instance a plaque rupture is not related to the presence of coronary artery disease. We think more studies with dobutamine stress echocardiography must be undertaken and if cardiac event rate is low additional stress tests must be performed to "boost" the prognostic value[72].

In conclusion: dobutamine-atropine stress test provides information of 1) extent and site of coronary artery disease; 2) perioperative cardiac risk in patients undergoing major vascular surgery; 3) late cardiac events.

Table 7 Prognostic value of dobutamine stress test in patients with proven or suspected coronary artery disease

	No	No events	Se	Sp	+ PV	- PV	Event
Mazeika[70]	51	23	74	71	68	78	MI,UAP, CABG,PTCA
Marcovitz[71]	291	71	65	55	32	83	CD,MI
Poldermans	430	83	60	62	27	87	CD,MI,UAP

Sens = sensitivity %; Spec = specificity %; PV = predictive value %; MI = myocardial infarction; UAP = unstable angina pectoris; CABG = coronary artery bypass surgery; PTCA = percutaneous transluminal coronary angioplasty.

Acknowledgements

We are indebted to Jos RTC. Roelandt, PhD, for reviewing the manuscript.

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CHAPTER 3

SAFETY OF DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHY IN PATIENTS WITH SUSPECTED OR PROVEN CORONARY ARTERY DISEASE[1]

(Short title: Dobutamine-atropine stress echocardiography)

Don Poldermans*, MD, Paolo M Fioretti, MD, Eric Boersma, BSE, Tamas Forster, MD, Hero van Urk*, MD, Jan H Cornel, MD, Mariarosaria Arnese, MD, Jos RTC Roelandt, MD

From the Thoraxcenter and Department of Vascular Surgery*, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam.

Abstract

The main purpose of this study was to establish the safety of high dose dobutamine-atropine stress echocardiography in patients with suspected or proven coronary artery disease. 650 consecutive examinations were completed. Mean age of patients was 61 years, 300 had a previous myocardial infarction.

Heart rate increased from 73 to 129 bpm during stress test, blood pressure did not change significantly (from 140/81 mmHg to 150/80 mmHg). Atropine was added on top of dobutamine in 239 patients when no ischemia was induced with dobutamine alone and the peak heart rate was <85% of the theoretical maximal heart rate. Atropine was more frequently used in patient on beta blockers (77% vs 27%, p <0.001). New wall motion abnormalities occurred in 243 (37%) cases. Significant and/or symptomatic cardiac tachyarrhythmias occurred in 24 examinations: one patient developed ventricular fibrillation, 3 patients developed sustained ventricular tachycardia; 12 patients experienced

[1] Am J Cardiol, accepted for publication

non-sustained ventricular tachycardia (less then 10 beats) and 8 patients had paroxysmal atrial fibrillation. Cardiac arrhythmias were more frequent in patients with a history of ventricular arrhythmias (ventricular tachycardia and fibrillation) (odds ratio 9.9, 2.0-45) or left ventricular dysfunction at rest (wall motion score of ≥1.12) (odds ratio 2.9, 1.1-7.6), but not associated with atropine addition. No death or myocardial infarction occurred.

In 13 cases, the full dose was not given despite absence of signs or markers of ischemia for limiting side effect, yielding an overall feasibility of the stress test of 98%.

Conclusion: dobutamine-atropine stress echocardiography is a relative safe and highly feasible test, with few side effects, having the highest risk of significant arrhythmias in patients with a history of ventricular arrhythmias and/or left ventricular dysfunction.

Introduction

Dobutamine-atropine stress combined with echocardiography was recently proposed for the diagnosis of coronary artery disease[1]. The test provides diagnostic and prognostic information[2-4]. High dose dobutamine is potentially arrhythmogenic, hypotension has been reported to occur and the safety of adding atropine to potentiate the test has not yet been extensively reported. So far only the study of Mertes et al.[5] has described the results of a large series of patients, in terms of safety and hemodynamic effects of the test. The aim of the present study is of describing the safety, feasibility and side effects of dobutamine stress echocardiography in particular when atropine is used for the potentiation of the dobutamine stress test[1-3,6].

Methods

Patient characteristics: 652 examinations were attempted in 626 consecutive patients (494 men, mean age 61 years range 22-90) with known or suspected coronary artery disease. A previous myocardial infarction was present in 300 patients. Angina pectoris was present in 281 patients. Antianginal medication was not discontinued before the study, including beta blocker medication in 268 cases. Indication for examinations were: chest pain evaluation (440) and preoperative cardiac risk stratification before non-cardiac surgery (212).

Dobutamine stress echocardiography: The dobutamine stress echocardiography protocol was approved by the hospital ethics committee and was performed as previously described[1]. In short, after giving verbal informed consent, the patients underwent a resting two-dimensional precordial echocardiographic examination. Standard apical and parasternal views were recorded on video tape

and a 12 lead electrocardiography was recorded. Dobutamine was then administered intravenously by infusion pump, starting at 10 μg/kg/minute for 3 minutes, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/minute (stage 4), and continued for 6 minutes. In patients not achieving 85% of their age-predicted maximal heart rate (in men (220-age) X 85%, in female (200-age) X 85%) who had no symptoms or signs of ischemia, atropine (starting with 0.25 mg increasing to a maximum of 1 mg) was given intravenously at the end of stage 4, while dobutamine was continued. Throughout dobutamine infusion the electrocardiogram was continuously monitored, the 12 lead electrocardiogram was recorded each minute and the blood pressure was measured by sphygmomanometry every 3 minutes. The two-dimensional echocardiogram was continuously monitored and recorded on video tape during the final minute of each stage. Quad screen display for side by side examination of rest and stress images have become routine during the last 200 studies. Metoprolol was available and used (1 to 5 mg. i.v.) to reverse the effects of dobutamine or dobutamine-atropine combination if these did not revert spontaneously and quickly. Atropine was also used as an antidote if bradycardia occurred after dobutamine. Off-line assessment of echographic images was performed by 2 experienced investigators without knowledge of the patients' clinical data but with knowledge of the doses of dobutamine and atropine used. For this semi-quantitative assessment the left ventricular wall was divided into 14 segments[7] and each was scored using a 4 point scale: 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic. Wall motion score index at rest (total score divided by the number of assessable segments) was calculated for each patient. An increase in score between rest and stress in 1 or more segments, that is a new or worsened wall motion abnormality, constituted a positive test.

Interruption criteria for the test were: a horizontal or downsloping ST depression >2mm at 80 ms after the J point, ST elevation, significant chest pain, reduction in systolic blood pressure >40 mmHg from that at rest or a systolic blood pressure less then 100 mmHg, significant cardiac arrhythmias, or any side effect regarded as being due to dobutamine. A new wall motion abnormality was considered as an interruption criteria in absence of side effects or other markers of ischemia only if it was severe and extensive.

Statistical analysis: Univariate analysis for categorial variables was performed using the chi-square test with Yates correction or Fisher's exact test. Continuous variables were analyzed using Student's t test. The difference in risk was expressed as the odds ratio (O.R.) with the corresponding 95% confidence intervals (C.I.). Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level. To compare and visualize the predictive value for cardiac arrhythmias of wall motion score index at rest, we used receiver operator characteristics curves.

Results

The dobutamine-atropine stress test was attempted 652 times. In 13 cases the test was nondiagnostic because it was prematurely stopped despite absence of signs or markers of ischemia for limiting side effects (chills (6), hypotension (2), hypertension (1), cardiac arrhythmias (2) and poor echo images (2)), yielding an overall feasibility of the test of 98%. There were no deaths or myocardial infarctions.

In 587 (90%) tests target heart rate (85% of theoretic maximal heart rate) was reached. In 63 examinations the test was stopped because of: 1) severe chest pain in 30 cases (4.6%), 2) electrocardiography changes in 9 patients (1.4%), 3) new wall motion abnormalities in 1 study (0.2%), 4) hypertension (systolic blood pressure ≥220 mmHg) in 1 case (0.2%), 5) hypotension (systolic blood pressure decrease >40 mmHg compared to base line) in 4 cases (0.6%), 6) cardiac arrhythmias (1 ventricular fibrillation, 3 sustained ventricular tachycardia and 8 paroxysmal atrial fibrillation) in 12 patients (1.9%) and chills in 6 cases (0.9%).

Patients were divided into 2 groups, the first group (N = 411) receiving dobutamine alone and the second group (N = 239) receiving dobutamine plus atropine. A comparison of clinical characteristics, side effects and reasons for stopping the test in the two groups are presented in tables 1 and 2.

Table 1 Clinical characteristics in patients with and without atropine

Clinical data	Group I N = 411	Group II N = 239	
Age (yrs) ± SD	63 ± 12	58 ± 12	p = 0.0001
			O.R. 95%, C.I.
Beta blockers	110 (27%)	158 (66%)	5.4, 3.8-7.9
History of angina	165 (40%)	116 (48%)	1.3, 0.9-1.8
History of infarction	184 (45%)	116 (48%)	1.1, 0.6-1.7
Diabetes mellitus	33 (8%)	19 (8%)	1.0, 0.5-1.9
Sex ♂	308 (75%)	186 (78%)	0.9, 0.6-1.3

Group I = stress test with dobutamine alone; Group II = dobutamine stress test with atropine addition; O.R. = odds ratio; C.I. = confidence interval.

Atropine was more often used in patients on beta blocker medication (O.R. 5.4, 95% C.I. 3.8-7.9) in patients on vs off beta blockers.

One or more markers of ischemia were detected during the test in a substantial proportion of patients: an ischemic ST depression (≥1 mm) was documented in 151 (24%) cases, ST elevation in 57 (9%) cases. Chest pain in

145 (22%) cases and new or worsening wall motion abnormalities in 243 (37%) patients.

Hemodynamic changes during dobutamine-atropine stress test: Heart rate and blood pressure values during stress test are listed in table 3. There was no significant change in blood pressure during peak stress.

Table 2 Comparison side effects and reasons for stopping stress test in patients with and without atropine

	Group I N = 411	Group II N = 239	O.R. 95% C.I.
Side effects			
Arrhythmias	15 (3.6%)	9 (3.7%)	1.1, 0.4-2.8
Chills	7 (1.7%)	5 (2%)	1.1, 0.3-2.7
Hypotension 20-40 mmHg	23 (5.6%)	7 (2.9%)	0.8, 0.4-1.5
>40 mmHg	2 (0.5%)	2 (0.8%)	1.4, 0.5-3.7
Hypertension	1 (0.2%)	0	
Interruption criteria			
Target heart rate	379 (92%)	214 (90%)	1.2, 0.7-2.3
Hypotension >40 mmHg	2 (0.5%)	2 (0.8%)	1.8, 0.2-12
Arrhythmias	6 (1.4%)	6 (2.5%)	1.7, 0.5-5.4
Angina pectoris	19 (4.6%)	11 (4.6%)	1.2, 0.8-1.7
ECG changes	3 (0.7%)	6 (2.5%)	1.1, 0.8-1.5
NWMA	1 (0.2%)	0	
Hypertension	1 (0.2%)	0	

Group I = stress test with dobutamine alone; Group II = dobutamine stress test with atropine addition; O.R. = odds ratio; C.I. = confidence interval; arrhythmias = ventricular fibrillation, sustained ventricular tachycardia (more then 10 beats), non sustained ventricular tachycardia (less then 10 beats) and paroxysmal atrial fibrillation; ECG = electrocardiographic changes; NWMA = new wall motion abnormalities; hypotension = decrease of systolic blood pressure compared to baseline.

Side effects: Hypotension and cardiac arrhythmias were the two most observed side effects of the stress test.

Hypotension, when defined as a decrease of systolic blood pressure of >20 mmHg compared to base line, occurred in 34 (5.2%) examinations. Though most patients were able to continue the test without discomfort, in 4 patients the test was stopped because of severe hypotension (decrease of systolic blood pressure >40 mmHg). There was no correlation between hypotension and

clinical data or stress test results but patients with concurrent beta blocker medication had significant less hypotension (O.R. 4.1, 95% C.I. 2.1-8.7). Hypotension was not related to the dose of dobutamine (O.R. 0.8, 95% C.I. 0.4-1.7) nor was it alleviated by the addition of atropine (O.R. 1.2, 95% C.I. 0.7-2.1). In 7 patients with systolic blood pressure decrease of 20 mmHg during top dose of dobutamine atropine was added without inducing more side effects compared to a similar group of 23 patients without atropine (O.R. 1.2, 95% C.I. 0.3-5.0).

Table 3 Hemodynamic effects of dobutamine-atropine stress test

	group I (N = 411)	group II (N = 239)
heart rate (bpm)		
rest	75 ± 14	66 ± 12*
dobutamine	129 ± 19	95 ± 22*
dobutamine + atropine	-	129 ± 18#
systolic blood pressure (mmHg)		
rest	142 ± 25	135 ± 22*
dobutamine	153 ± 32	146 ± 25*
dobutamine + atropine	-	149 ± 27#
diastolic blood pressure (mmHg)		
rest	82 ± 13	79 ± 12@
dobutamine	79 ± 17	72 ± 21*
dobutamine + atropine	-	78 ± 13#

Group I = stress test with dobutamine alone; Group II = dobutamine stress test with atropine addition; data are expressed as mean ± SD; C.I. = confidence interval; heart rate (beats/minute); * p value <0.001 between group II and I at the same stage; # no significant difference between peak dobutamine (group I) / dobutamine+atropine(group II); @ p value = 0.02 between group II and group I at the same stage.

Significant and/or symptomatic cardiac tachyarrhythmias occurred in 24 examinations: besides arrhythmias leading to interruption of the test, 12 patients experienced non-sustained ventricular tachycardia. Premature ventricular complexes occurred in 64 examinations and was not considered as a serious side effect. The patient with ventricular fibrillation had previous symptomatic ventricular arrhythmias and myocardial infarctions. Wall motion score index at rest was 1.56. During dobutamine infusion (40 μg/kg/min) this patient developed new wall motion abnormalities rapidly followed by ventricular

fibrillation and was successfully resuscitated (one single counter-shock) without evidence of a new cardiac infarction. Sustained ventricular tachycardia occurred in 12 cases, at heart rate of 160-180 bpm, lasting no more then 2 minutes, abated by metoprolol instantly in 2. There was no recurrence in the hours after the test.

The incidence of dobutamine induced cardiac arrhythmias was increased in patients with a history of previous ventricular arrhythmias (ventricular tachycardia or fibrillation) (O.R. 9.9, 95% C.I. 2.0-45) and rest wall motion abnormalities, defined as a resting with wall motion score index ≥1.12 (O.R. 2.9, 95% C.I. 1.1-7.6). Other stress test results, including the "ischemic" signs or markers were not predictive for arrhythmias. There was no correlation between atropine addition and arrhythmias (O.R. 1.2, 95% C.I. 0.4-3.3). Bradycardia occurred in 2 patients accompanied by hypotension, both with stress-induced inferior wall ischemia. Both patients were given atropine (0.25 mg/i.v.) and recovered without complications.

Discussion

Dobutamine-atropine stress is a new and promising test for detection of coronary artery disease. In 652 examinations the test was not completed in 16 cases despite absence of signs or markers of ischemia for limiting side effects, yielding an overall feasibility of 98%. These results are comparable with dipyridamole echocardiography[8], which showed a feasibility of 99%.

Target heart rate as test end-point was reached in 90% of the examinations. This is higher compared to other studies as Mertes et al.[5] were target heart rate is achieved in 52% and Mazeika et al.[9] in 18%. This can be partly explained by a different stress protocol because there was no interruption for 1) "moderate" hypotension (decrease in systolic blood pressure ≥20 - <40 mmHg compared to baseline), 2) new wall motion abnormalities unless severe and extensive or accompanied by other markers of ischemia, and atropine was used always in patients who fail to reach test end-point (target heart rate or any sign or marker of ischemia). Despite this more "aggressive" approach there were no fatal complications or myocardial infarctions.

Side effects consisted mostly of hypotension and cardiac arrhythmias. Hypotension, if defined as a decrease of systolic blood pressure of >20 mmHg, is the most frequent side effect (34 examinations), leading to a premature end of the test in only 4 instances in which systolic blood pressure decreased >40 mmHg compared to baseline value. A systolic blood pressure decrease of ≥20 - <40 mmHg during the test has not been considered by us as a serious side effect of the test, in contrast to others[9,10]. In our experience there were no complications as long as the patient is monitored closely and can be given atropine safely if the target heart rate is not reached with dobutamine alone.

Possible mechanisms of dobutamine-atropine induced hypotension are 1) poor left ventricular function during stress because of extensive wall motion abnormalities 2) vasodilator effect of dobutamine 3) development of subaortic stenosis 4) atropine administration 5) vasodepressor reflex induced by myocardial vigorous myocardial contractions as suggested by Mazeika et al.[12]. Our findings support options 2 and 5. Similar to others[11,13], we observed that hypotension occurred less frequently in patients on beta blockers.

Cardiac arrhythmias are the second most noted side effects. Our study shows an incidence of significant arrhythmias (ventricular fibrillation, sustained/nonsustained ventricular tachycardia, atrial fibrillation/atrial flutter) of 24 (3.6%), similar to the study of Mertes et al.[5], who found a incidence of 48/1118 (4.3%). There was a strong relation between a history of previous ventricular arrhythmias (ventricular tachycardia or fibrillation) or diffuse rest wall motion abnormalities, (both indicating a poor left ventricular function) and cardiac arrhythmias during the test. There was no correlation with signs or markers of ischemia during the test nor with the addition of atropine.

In conclusion, dobutamine-atropine stress echocardiography is a safe and feasible test. Some caution should be used in patients with a history of ventricular arrhythmias or poor left ventricular function at rest, in whom the test may induce serious arrhythmias. In these patients comparative studies with other stress modalities like dipyridamole are required.

We acknowledge Bas van der Borden for developing the database.

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CHAPTER 4

ATROPINE INCREASES THE ACCURACY OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN PATIENTS TAKING BETA BLOCKERS[1]

(Short title: Influence of beta blockers on dobutamine stress echocardiography)

Paolo M Fioretti, MD, FESC, Don Poldermans, MD,
Alessandro Salustri, MD, Paolo Bellotti, MD, Tamas Forster, MD,
Eric Boersma, BSE, Albert J McNeill, MD, El-Said M El-Said, BCh, MS,
and Jos RTC Roelandt, MD, FACC

From the Thoraxcenter, University Hospital Rotterdam-Dijkzigt, Rotterdam, the Netherlands.

Abstract

Background: Dobutamine-atropine stress echocardiography is used for the non-invasive diagnosis of coronary artery disease. Beta blockers may influence stress test results. The aim of this study was to assess if atropine addition can compensate for the presence of beta blockers in dobutamine stress echocardiography.
Methods and Results: Twenty-six patients referred for evaluation of chest pain were studied twice, on and off metoprolol 100 mg b.i.d. (in random order sequence) with at least a 48 hr wash out period. Dobutamine stress echocardiography was performed using up to 40 μ/kg/min, if necessary followed by the addition of atropine to achieve 85% of the age predicted maximal heart rate unless symptoms or markers of ischemia appeared.
Atropine was given to patients on beta blockers more often [(22/26) vs (6/26)] than to patients off beta blockers ($p < 0.01$). Heart rate in every stage of the test

[1] Eur Heart J, accepted for publication

was lower on beta blockers. Chest pain occurred on beta blockers significantly less compared to off beta blockers (8% vs 46%). After atropine there was no significant difference (31% vs 46%.). During dobutamine stress new wall motion abnormalities occurred in 3 patients on beta blockers (12%), increasing to 15 patients after adding atropine (57%). New or worsened wall motion abnormalities occurred in 12 patients (46%) off beta blockers with dobutamine alone and in 14 patients after adding atropine (53%).
Conclusions: 1) beta blockers decrease the chronotropic effect and reduce the incidence of myocardial ischemia during dobutamine stress, 2) the addition of atropine to dobutamine increases heart rate and equalizes the detection of ischemia in patients on and off beta blockers.

Key-words: Dobutamine-atropine stress echocardiography, beta blocker agents.

Introduction

Pharmacological stress tests in conjunction with echocardiography are becoming increasingly popular for inducing myocardial ischemia in patients with suspected or proven coronary artery disease. It has been recently shown that dipyridamole echocardiography is negatively affected by the use of antianginal medication[1,2]. Patients referred for evaluation are often on antianginal medication including beta blockers, and it may be impractical or even dangerous to stop these before the test. Dobutamine stress echocardiography is a novel method for assessing patients with suspected coronary artery disease[3,4]. Although it seems likely that beta blockers would negatively influence the diagnostic accuracy of the test, being partial antagonists of dobutamine[5], it has been recently suggested that this does not occur[6].

However this conclusion is based on a single study performed on patients on different medications with different degrees of coronary artery disease, and can only be considered tentative. Therefore we prospectively tested the hypothesis that the use of beta blockers reduces the incidence of myocardial ischemia in patients with chest pain referred for dobutamine stress echocardiography. A secondary aim of the study was to assess the utility of atropine in increasing the detection of myocardial ischemia in those patients who did not achieve adequate heart rate or evidence of ischemia at peak dobutamine doses.

Methods

Patient selection: Between May and July 1991, 26 patients underwent dobutamine stress echocardiography at Dijkzigt University Hospital. All patients were referred for the diagnosis of chest pain and were physically unable to

perform an adequate exercise test. Fifteen patients also underwent coronary angiography. Two patients had previous coronary artery bypass grafting. The mean age was 61 years (range 45-72 years) and 21 were men. Sixteen patients had a history of a previous myocardial infarction.

Study protocol: After giving verbal consent, all patients were studied both on and off beta blockers (metoprolol 100 mg b.i.d.) in random order sequence. If the first test was done on beta blockers, which were given for at least 4 days, there was a wash out period of at least 48 hr. The average interval between the 2 tests was 4.5 days (range 3-7 days). Other medications (nitrates in 3 patients and calcium antagonists in 2 patients) were kept constant during the two studies. The dobutamine stress echocardiography protocol was approved by the hospital ethics committee.

Dobutamine stress test: Dobutamine was administered intravenously beginning at a dose of 10 μgr/kg/min. Thereafter, the dose was increased by 10 μgr/kg/min increments every 3 minutes, up to a maximum of 40 μgr/kg/min (stage 4) for up to 6 minutes. Atropine was administered at the end of stage 4 in those patients who did not achieve 85% of age predicted maximal target heart rate, starting with 0.25 mg iv and repeated up to a maximum of 1.0 mg within 4 minutes with continuation of dobutamine rate unless the test was positive with dobutamine alone.

Throughout dobutamine infusion the ECG was continuously monitored, the 12 lead ECG was recorded each minute in left lateral decubitus position. Chest electrodes were sometimes slightly shifted to get the best echocardigraphic window, and the position was not changed during the test. Blood pressure was measured by sphygmomanometry every 3 minutes. Indications for terminating the test were: obvious new wall motion abnormalities by echo, ST depression >2 mm at 80 ms after the J point, ST elevation >2 mm, significant chest pain, reduction in systolic blood pressure >40 mm Hg from that at rest, or any serious side effects regarded as being due to dobutamine. Metoprolol was available and used to reverse the effects of dobutamine or dobutamine combined with atropine, if they did not revert spontaneously and quickly.

Echocardiography: with the patient in left lateral decubitus position, two dimensional echocardiograms were obtained. Standard apical and parasternal views were recorded on video tape. At the last minute of every stage of the test a recording was made. Review of the tape was performed by 2 experienced investigators blinded to the beta blocker status of the patients. In case of disagreement between the 2 reviewers, a third investigator without knowledge of previous assessments viewed the images and a consensus was achieved. In previous work we have already shown an excellent inter and intra observer reproducibility of the interpretation of stress echocardiographies of 91 and 92%[7]. In addition, the reproducibility of wall motion abnormalities during dobutamine-atropine stress echocardiography was 100% in 23 patients who underwent serial studies on different days[8].

For these semiquantitative assessments, the left ventricular wall was divided into 14 segments[9], and each segment was scored using a 4-point scale: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. The 14 segments were combined into 5 myocardial areas: anterior, septal, lateral, inferior and apex. An increase in score in 1 segment or more from rest to stress constituted a positive test. The score of each segment is presented at rest and during peak stress. When these results are analyzed it should be remembered that during dobutamine stress some segments may improve while others may deteriorate, the total score may not change despite regional ischemia.
Coronary arteriography: 15 patients already underwent cardiac catheterization (Judkins technique) requested by their referring physicians for chest pain (all performed within three months of study entering). Coronary artery anatomy was assessed visually by 2 experienced investigators. A vessel was considered to have significant obstruction if its diameter was narrowed by 50% or more. The presence of collateral blood flow distal to the stenosis was investigated in every patient.
Statistical analysis: results are expressed as mean +- standard deviation, and 95% confidence intervals are given where appropriate. The difference between the continuous and discrete variables are calculated by paired and unpaired Student's t test, and by means of chi square test for the discrete variables. A probability of less than 5% was considered significant.

Results

Twenty-six patients undergoing dobutamine stress echocardiography were included in the study and investigated twice on and off beta blockers in random order sequence. Clinical data and the results of the dobutamine stress test and coronary arteriography are presented in table 1. Atropine was added according to the protocol in order to reach target heart rate in 22/26 patients on beta blockers, compared to 6/26 off beta blocker medication ($p < 0.001$).
Hemodynamic changes: resting heart rate on beta blockers was lower (60 ± 8 bpm vs 73 ± 12 bpm ($p < 0.001$)) and remained so throughout the study at peak dobutamine dose (86 ± 17 bpm vs 124 ± 22 bpm ($p < 0.001$)) and at dobutamine combined with atropine (124 ± 15 bpm vs 143 ± 12 bpm ($p < 0.001$)) (figure 1). Beta blockers did not significantly effect systolic blood pressure at rest (153 ± 23 mm Hg vs 153 ± 23 mm Hg(NS)), at peak dobutamine (145 ± 24 mm Hg vs 159 ± 27 mm Hg(NS)) or at dobutamine combined with atropine (153 ± 23 mmHg vs 156 ± 30 mmHg(NS)) (table 2).

Angina pectoris: chest pain occurred without beta blockers during dobutamine infusion in 12 patients (46%, CI 0.27-0.65), not influenced by atropine. Beta blockers reduced the incidence of chest pain during dobutamine infusion,

occurring in 2 patients (8%, CI 0.00-0.18)) but increasing after atropine to 8 patients (31%, CI 0.13-0.49) (table 2).

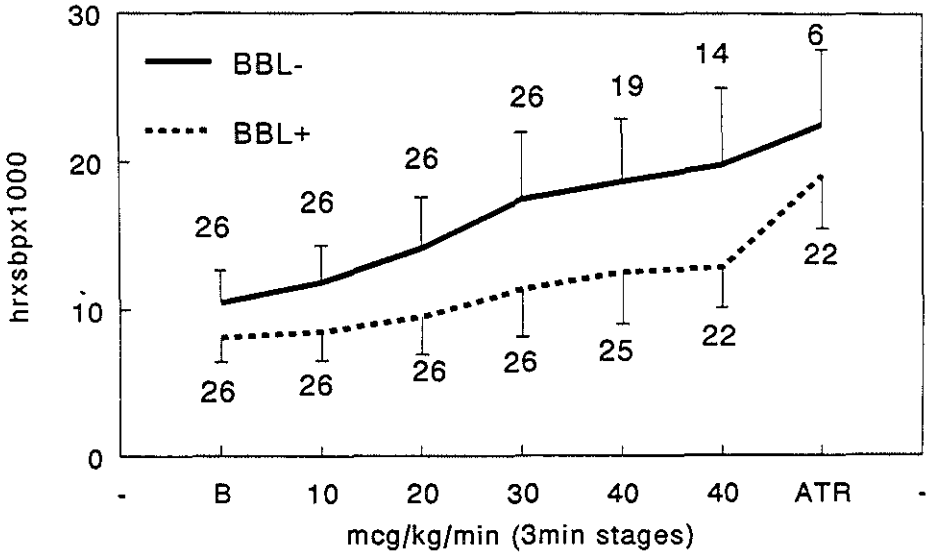

Figure 1 Heart rate (beats per minute) during dobutamine-atropine stress test. Number of patients tested at every stage indicated; BBL- = off beta blockers; BBL+ = on beta blockers

Table 2 Hemodynamic data of dobutamine stress test (mean ± SD)

	No beta blockers	Beta blockers	P-value
Baseline systolic blood pressure (mmHg)	144 ± 23	153 ± 23	NS
Peak dobutamine systolic blood pressure (mmHg)	159 ± 27	145 ± 24	NS
Dobutamine + Atropine systolic blood pressure (mmHg)	156 ± 30	153 ± 23	NS
Baseline heart rate (beats/min)	73 ± 12	60 ± 8	0.001
Peak dobutamine heart rate (beats/min)	124 ± 22	86 ± 17	0.001
Dobutamine + Atropine heart rate (beats/min)	143 ± 12	124 ± 15	0.001

NS = not significant.

Electrocardiographic changes: ischemic ST segment changes, (depression or elevation >0.1 mV) occurred off beta blockers during dobutamine infusion in 10 patients (38%, CI 0.19-0.57), increasing after atropine to 12 patients

(46%, CI 0.27-0.65). Ischemic ST changes occurred in 4 patients (15%,CI 0.01-0.31) on beta blockers after dobutamine alone, increasing to 10 patients (38%, CI 0.19-0.57) after adding atropine (figure 2)

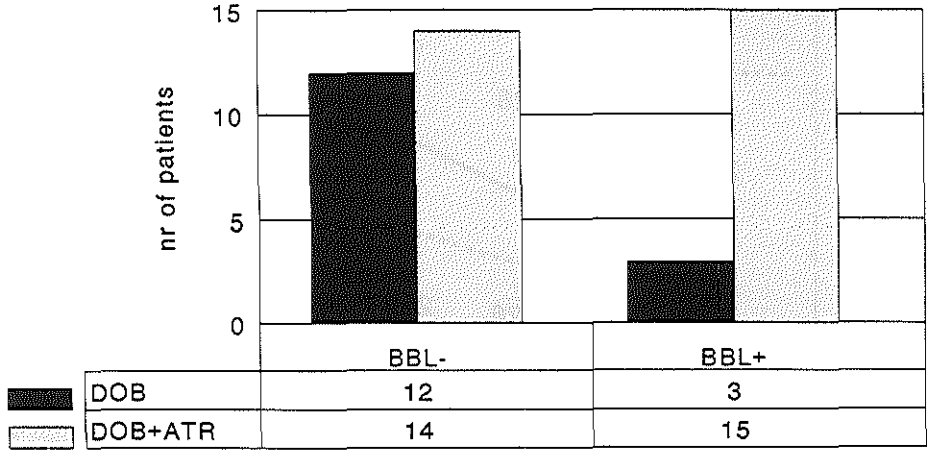

Figure 2 Chest pain during dobutamine-atropine stress test; Dob = dobutamine; Atr = atropine; BBL- = off beta blockers; BBL+ = on beta blockers

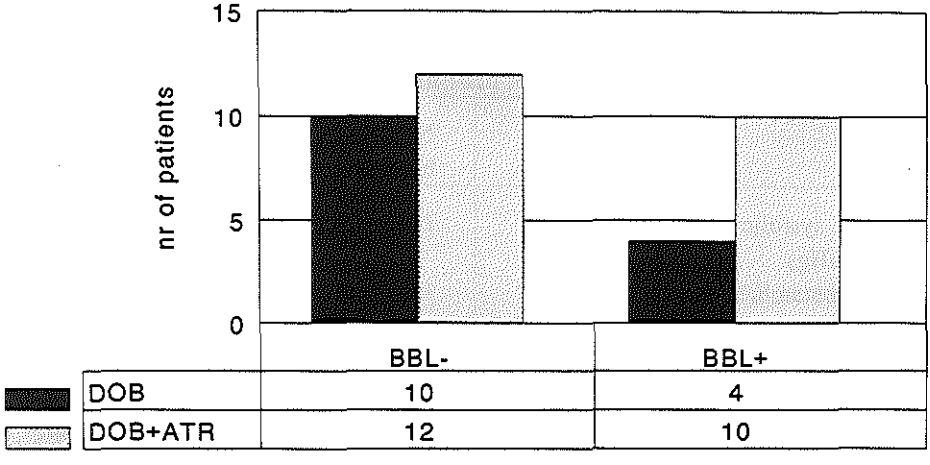

Figure 3 New wall motion abnormalities during dobutamine-atropine stress test; Dob = dobutamine; Atr = atropine; BBL- = off beta blockers; BBL+ = on beta blockers

Echocardiographic changes: new wall motion abnormalities (NWMA) during dobutamine infusion occurred off beta blockers in 12 patients (46%, CI 0.27-0.65) and in 14 patients after addition of atropine (53%, CI 0.31-0.69). On beta-blockers during dobutamine 3 patients had NWMA (12%, C.I. 0.00-0.24) and

in 15 patients after addition of atropine (57%, C.I. 0.33-0.71) (figure 3). Wall motion score at peak stress (including atropine) was similar in patients on and off beta blockers (1.24 ± 0.25 vs 1.22 ± 0.22).

Coronary arteriography was performed in 15 patients all with significant coronary disease. The sensitivity of dobutamine-atropine echocardiography was similar on (10/15) and off beta blockers (10/15).

Side effects: no serious side effects were present in these patients. Metoprolol was given during the test in 9 patients to terminate angina and/or tachycardia, of which 8 were off beta blockers.

Discussion

Dobutamine stress echocardiography is increasingly used as a non-invasive diagnostic tool for eliciting myocardial ischemia in patients with suspected coronary artery disease. Since dobutamine is a strong beta adrenergic agonist the concomitant use of beta blockers may reduce the diagnostic power of dobutamine stress test. Many patients referred for functional evaluation of chest pain are on beta blockers, and it can be impractical to withdraw them abruptly; therefore it is of clinical relevance to assess the extent to which the dobutamine stress test is affected by the use of beta blockers. As far as we are aware, this is the first prospective cross over study to address this question.

The main findings of the present study are twofold: first, beta blockers blunt the chronotropic effect of dobutamine and significantly reduce the incidence of clinical and echocardiographic markers of myocardial ischemia during dobutamine stress test. Second the addition of atropine to the peak dose of dobutamine compensates for the presence of beta blockers by increasing the heart rate and, more importantly, increasing the incidence of myocardial ischemia by echocardiography. It seems therefore likely that the positive chronotropic effect of atropine is able to potentiate the inotropic and chronotropic effect of high dose dobutamine.

Coronary arteriography was performed in 15 patients, all of whom had significant coronary artery disease, (stenosis >50%). Collateral blood supply was present in 9 patients, 4 of whom had NWMA during stress. Absence of collateral circulation was seen in 6 patients, all of whom had NWMA during stress. These numbers are too low to permit statistical analysis but confirm the ability of dobutamine stress echocardiography to detect significant coronary disease, as has been stated by others[10,11,12]. The sensitivity of the dobutamine-atropine test for detecting coronary artery disease was similar in patients on and off beta blockers (10/15 vs 10/15).

In previous studies we found good reproducibility of dobutamine stress echo findings[7,8]. Therefore the different findings in patients on and off beta blockers in this study are likely not related to day to day or interobserver and intraobserver variability.

This study represents an extension of previous data from our laboratory[12], which suggest that atropine addition might increase the diagnosis of coronary artery disease in patients failing to achieve adequate heart rate on high dose dobutamine. In those previous studies we also reported the safety and the paucity of side effects of such "potentiated" dobutamine stress test. Our experience has recently been confirmed by others[13,14].

Importantly in the present study we found that by adding atropine to dobutamine, the end-point of the test (ischemia and/or 85% of the age predicted maximal heart rate) could be reached in a similar number of patients both on beta blockers (25/26) and off beta blockers (25/26).

Recent results from Sawada et al.[6] and Marcovitz et al.[4] suggest that beta blockers do not influence the sensitivity of dobutamine stress echocardiography. These studies are not comparable to our study for several reasons: their definition of a positive test was more "liberal" (including a lack of improvement of wall thickening as a criterium for positivity), the dose of beta blockers, "fixed" in our patients, was not specified and, the patients were not studied both on and off beta blockers. Since patients were studied only once, it cannot be excluded that the similar stress test results for patients on and off beta blockers was due to a greater severity of coronary artery disease in patients taking beta blockers.

It has been recently demonstrated that beta blockers also reduce the sensitivity of dipyridamole stress echocardiography[2], probably via reduced myocardial oxygen consumption.

Similar to the findings of the present study, Picano et al.[15] suggest that the addition of atropine to dobutamine enhances the detection of myocardial ischemia without increasing the risk of the procedure.

As a limitation of the present study we must acknowledge that we cannot provide a judgement on the specificity of dobutamine-atropine stress test, since no patients with normal coronary arteries were included in the study. However in a previous study[12] we have already demonstrated that the addition of atropine to detect coronary artery disease does not decrease the specificity of the test. Another potential limitation is that no side by side digital analysis of echo images was performed at the time of the study. However we have previously shown, even if more cumbersome, the diagnostic information from video-tape is similar to that derived from cine-loop[10].

In conclusion, this study shows that beta blockers reduce the ability of high dose dobutamine to induce myocardial ischemia during stress echo. However, the addition of atropine can overcome this limitation and should therefore be recommended in every of our currently negative dobutamine stress test.

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Table 1 Baseline characteristics, results of dobutamine stress test and coronary arteriography

Pat/Sex	BBL	Age	MI	HR	HR/A	SBP	SBP/A	REST/WMSI	PEAK/WMSI	Loc isch.	Angio	Coll	AP	ST
1/M	-	51	+	143		170		1.0	1.14	P	3VD	-	+	+
	+			75	118	130	150	1.07	1.14	P			-	-
2/M	-	58	+	114	147	100	110	1.21	1.56	A/L/Ap	LAD	+	-	-
	+			110	150	125	150	1.28	1.56	A/L/Ap			-	-
3/M	-	53	-	134		170		1.21	1.35	P	LCX	-	+	+
	+			110	138	160	170	1.07	1.14	P			-	+
4/M	-	49	-	145		150		1.28	1.28		RCA	+	-	+
	+			83	129	140	140	1.28	1.28				-	-
5/M	-	60	+	136		180		1.0	1.07	SA	LAD	-	-	-
	+			109	130	180	180	1.0	1.14	SA			-	-
6/M	-	41	+	133	153	153	144	1.14	1.14	SA/SP	2VD	-	-	+
	+			70	122	128	153	1.28	1.42	Lat			-	+
7/M	-	69	-	146		162		1.0	1.0		LAD	+	-	-
	+			135		140		1.0	1.0				-	-

8/M	-	70	+	130		157		1.56	1.49	SA	2VD	-	-	-
	+			75	128	158	128	1.70	1.70	SA			-	-
9/M	-	49	-	137	145	144	157	1.0	1.0		LCX	+	+	-
	+			87	130	148	167	1.0	1.0				+	-
10/F	-	63	+	136		150		1.28	1.28		RCA	+	-	-
	+			88	119	110	110	1.42	1.42				-	-
11/M	-	42	+	58	153	140	197	1.14	1.14		RCA	+	-	-
	+			75	140	143	152	1.14	1.14				+	-
12/F	-	52	-	130		169		1.0	1.0				+	-
	+			73	130	153	159	1.0	1.0				+	-
13/M	-	68	+	143		108		1.14	1.21	P	RCA	+	-	-
	+			100	143	114	110	1.0	1.07	P			-	-
14/M	-	67	+	136		162		1	1.14	SA/SP	1VD	+	+	+
	+			62	95	128	135	1	1.14	SP			+	+
15/M	-	68	-	96	120	170	150	1.14	1.21	P	RCA	+	+	+
	+			80	85	180	200	1.0	1.07	P			+	+

Pat/Sex	BBL	Age	MI	HR	HR/A	SBP	SBP/A	REST/WMSI	PEAK/WMSI	Loc isch.	Angio	Coll	AP	ST
16/F	-	71	+	143		140		1.49	1.56	Lat	RCA	-	+	+
	+			78	108	140	160	1.49	1.56	Lat			-	-
17/F	-	67	-	120	144	180	180	1.14	1.28	P			+	-
	+			85	133	163	190	1.42	1.49	P			+	+
18/F	-	72	+	117		176		1.70	1.84	SA			-	-
	+			86	120	157	172	1.84	1.91	SA/SP			-	-
19/M	-	55	+	132		160		1.56	1.56				+	+
	+			98	127	130	120	1.56	1.56				+	+
20/F	-	51	-	121		190		1.0	1.0				-	-
	+			75	135	190	170	1.0	1.0				-	-
21/M	-	66	+	96		160		1.07	1.07				-	-
	+			98		140		1.07	1.14	P			-	+
22/M	-	45	+	124		180		1.0	1.07	P			-	+
	+			102		180		1.0	1.07	P			-	+
23/M	-	56	-	136		160		1.07	1.14	P			-	-
	+			94	130	140	150	1.07	1.14	P			-	+

24/M	-	51	-	118		230		1.0	1.0				-	-
	+			104		210		1.0	1.0				-	-
25/M	-	50	+	140		150		1.07	1.07				+	-
	+			106	136	140	140	1.07	1.07				+	-
26/M	-	58	+	132		160		1.07	1.07				+	+
	+			98	127	130	120	1.07	1.07				+	+

BBL-/+ = off and on beta blocker; MI = previous myocardial infarction; HR = maximal heart rate during dobutamine (beats/min); HR A = maximal heart rate during dobutamine combined with atropine (beats/min); SBP = maximal systolic blood pressure during dobutamine (mmHg); SBP A = maximal systolic blood pressure during dobutamine combined with atropine (mmHg); REST = wall motion score index at rest; PEAK = wall motion score index during maximal doses dobutamine with or without atropine; Loc isch = location of new wall motion abnormalities; P = posterior wall; A = anterior wall; Ap = apex; SA = septum anterior; SP = septum posterior; L = lateral wall; Coll = presence of collateral blood supply; 3VD = stenosis of LAD, LCX and RCA; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; AP = angina pectoris; ST = electrocardiographic changes during test.

Table 3 Incidence of different markers of ischemia on and off beta blockers during dobutamine-atropine stress test

Allocation	No. pts	Angina Pectoris	95% C.I.	ST- changes	95% C.I.	NWMA	95% C.I.
BBL-							
without atropine	20	12 (46%)	0.27-0.65	10 (38%)	0.19-0.57	12 (46%)	0.27-0.65
with atropine	6	0		12 (46%)	0.27-0.65	14 (53%)	0.31-0.69
BBL+							
without atropine	4	2 (8%)	0.00-0.18	4 (15%)	0.01-0.31	3 (12%)	0.00-0.24
with atropine	22	8 (31%)	0.13-0.49	10 (38%)	0.19-0.57	(57%)	0.33-0.71

No pts = number of patients achieving test end-point; AP = number of patients with angina pectoris during test; ST = number of patient with electrocardiographic changes during test; NWMA = number of patients with new wall motion abnormalities; BBL-/+ = off or on beta blockers; CI = confidence intervals; %=percentage.

CHAPTER 5

CARDIAC CHRONOTROPIC RESPONSIVENESS TO ß-RECEPTOR STIMULATION IS NOT REDUCED IN THE ELDERLY[1]

(Short title: heart rate response to dobutamine infusion)

Don Poldermans*, MD, Eric Boersma, BSE, Paolo M. Fioretti, MD, PhD, Hero van Urk*, MD, PhD, Frans Boomsma**, PhD, Arie J. Man in 't Veld**, MD, PhD.

Cardiovascular Research Institute COEUR; Departments of Surgery*, Internal Medicine I** and Cardiology, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, the Netherlands.

Abstract

Background: The hypothesis of reduced cardiac ß-adrenoceptor responsiveness in the elderly is based on a smaller increase in heart rate after administration of isoproterenol, a non-selective $ß_1$ and $ß_2$-adrenoceptor agonist. The chronotropic response to isoproterenol is caused by stimulation of cardiac $ß_1$ and $ß_2$-adrenoceptors and baroreflex-induced vagal withdrawal, as a consequence of vascular $ß_2$-adrenoceptor mediated vasodilatation. In dobutamine-stress-echocardiography we were able to retest the hypothesis more accurately since dobutamine is a relatively selective $ß_1$-adrenoceptor agonist with weak $ß_2$-adrenoceptor and α-adrenoceptor stimulant activity, which prevent baroreflex mediated changes in heart rate.
Methods: Stepwise incremental infusions of dobutamine, 10, 20, 30 and 40 µg/kg/min were given. Each dose step lasted for 3 minutes. Infusions were stopped if a target heart rate (85% of the theoretical maximal age-related heart rate) was reached or side effects occurred. Hemodynamic responses to

[1] Submitted for publication

dobutamine are presented of those patients who did not use a ß-blocker and who had no side effects during stress test (n = 296). In each subject we calculated the dose of dobutamine required to increase heart rate by 50% of the maximum heart rate during the highest dose of dobutamine. In 15 patients plasma concentrations of dobutamine were measured during the test.
Results: No relationship was found between age and the sensitivity to dobutamine (n = 296). In "healthy" subjects i.e. those without diabetes, hypertension, angina, smoking or echocardiographic abnormalities at rest and during stress, (n = 54), an increased heart rate response to dobutamine was found in senescent subjects. This could be related to a reduced systolic blood pressure rise during dobutamine in the elderly. However in patients with overt dobutamine induced myocardial ischemia (n = 19), the sensitivity to dobutamine was indeed reduced without change in blood pressure. There were no significant age-related difference in plasma concentrations of dobutamine.
Conclusion: No evidence for a reduced ß-adrenoceptor responsiveness to dobutamine was found in the elderly patients, unless acute ischemia during dobutamine was present.

Introduction

Adrenergic responsiveness changes with human ageing[1-2]. Changes in responses to neurotransmitters may have important clinical consequences for drug-therapy in elderly patients. The ß-adrenergic receptor has been extensively studied by pharmacological and physiological examinations[3-6]. $ß_1$-Receptor activation induces a positive inotropic and chronotropic effect on the heart and $ß_2$-receptor stimulation induces vascular relaxation. The $ß_1$-adrenergic receptor is thought to become less sensitive with ageing. Evidence for this hypothesis is circumstantial: 1) basal concentrations of norepinephrine are increased in the elderly; 2) ß-adrenergic receptor densities and affinities are unchanged[2] and yet; 3) the chronotropic response to bolus infusions of isoproterenol (a $ß_1$-and $ß_2$-adrenoceptor stimulant) in older animals and senescent man is decreased[4,7,8]. In the elderly, the reduced effect of isoproterenol on heart rate may be caused by an attenuated direct chronotropic response mediated by $ß_1$- and $ß_2$-adrenoceptors, and/or a reduced activation of the baroreflex in response to vasodilatation induced by isoproterenol. In previous animal studies, mostly the rat, baroreflexes were intact and isoproterenol was given as bolus injections[7,8]. A study with pithed rats, eliminating the baroreflex response, found no difference in the chronotropic effect of isoproterenol in young and elderly rats[5].

Here we present a study on the chronotropic responsiveness to incremental stepwise infusion of dobutamine, a relatively selective $ß_1$-adrenoceptor agonist with weak α- and $ß_2$-adrenoceptor stimulant activity[9]. As a consequence dobutamine, in contrast to isoproterenol, does not evoke baroreflex-induced

changes in heart rate induced by vasodilatation[10]. Our analysis comes partly from previously published data on dobutamine-stress-echocardiography[11]. The data for patients with hypertension, diabetes mellitus, a previous myocardial infarction, angina pectoris, evidence for myocardial ischemia detected with echocardiography during dobutamine infusion and in smokers were analyzed separately.

Methods

Patient characteristics: Three hundred and twenty four patients were studied in 1992 and 1993 for dobutamine stress echocardiography. Patients on beta-blocker medication and those who experienced side effects during dobutamine infusion necessitating interruption of the test were excluded from this study, leaving a total number of 296 patients for analysis (214 men, mean age was 61 years, range 22-90). In 89 (30%) of the studies patients were older then 70 years. A history of previous myocardial infarction was present in 119 (40%), angina pectoris in 78 (26%) and diabetes mellitus (with drug therapy) in 31 (10%) cases. Hypertension, defined as sustained elevated diastolic blood pressure of ≥90 mmHg with or without drug treatment was present in 100 (34%) patients. Indication for examinations were: 112 (38%) evaluation of chest pain and 184 (62%) preoperative cardiac risk stratification[11].

In 15 patients dobutamine plasma concentrations were measured during the test in 10 men, mean age 61 ± 9 years (range 40-77).

Dobutamine stress test: The dobutamine stress protocol was approved by the Hospital Ethical Committee. After they had given informed consent, the patients underwent a resting two-dimensional echocardiographic examination. Dobutamine was administered intravenously with an infusion pump, starting at 10 μg/kg/min for 3 minutes, followed by stepwise increments of 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. The dobutamine infusion was stopped if a target heart rate (85% of a theoretical maximal heart (men (220-age) X 85%, women (200-age) X 85%) was achieved[12]. Blood pressure and heart rate were measured at rest and at the end of every infusion step with an automatic device (Accutorr A1, Datascope Corp., Paramus NY, USA). A 12-lead ECG was recorded at rest and at the end of every dose step. The two-dimensional echocardiogram was monitored continuously and recorded on video tape during the last minute of every dose step. Criteria for interruption of the test were: a horizontal or downsloping ST depression >2mm at 80 ms after the J point, ST elevation, severe continuous chest pain, reduction in systolic blood pressure >40 mmHg from baseline or a systolic blood pressure less then 100 mmHg, significant cardiac arrhythmias, or any side effect regarded as being due to dobutamine. A new wall motion abnormality was considered as an

interruption criteria in absence of side effects or other markers of ischemia only if it was severe and extensive[11].

Off-line assessment of echocardiographic images was performed by two investigators. Reduced wall thickening and new wall motion abnormalities are the hall marks of ischemia[13]. For semiquantitative assessment, the left ventricular wall was divided into 14 segments and each was scored on a four point scale: 1, normal; 2, hypokinetic; 3, akinetic and 4, dyskinetic. A new wall motion abnormality is defined as an increase in score between rest and stress.

Dobutamine measurement in plasma: Blood samples were taken at the end of every dose step. Dobutamine was measured in plasma as described by Alberts et al.[14] In brief, after a liquid-liquid extraction and derivatization with the fluorogenic agent 1,2-diphenylethylenediamine, dobutamine is measured by fluorometric detection after separation by HPLC-chromatography.

Statistical analysis: The effects of dobutamine on blood pressure was assessed by paired t-test. By linear regression analysis the slopes of the heart rate-log dose-response curves were calculated in each individual patient. The sensitivity for dobutamine was calculated as the $ED_{50\%}$-HR, which is the dose required to increase heart rate by 50% of the maximum at the highest dose of dobutamine. Dobutamine sensitivity in relation to the clinical variables (angina, previous infarction, hypertension, diabetes and smoking) and echocardiographically detected evidence for ischemia were compared by unpaired t-tests. "Healthy" individuals were defined as those without a history of any of the clinical variables (n = 54). Individuals with signs of acute ischemia during dobutamine stress were divided in three categories: 1) subjects with echocardiographic detected myocardial ischemia (n = 86); 2) subjects who also had electrocardiographic changes (n = 26) and 3) subjects who experienced angina during the test as well (n = 19). A 2-tailed p value <0.05 was required for significance. All data are expressed as mean ± 95% confidence interval, with the exception of age in the table which is presented as mean ± SD.

Results

Heart rate increased from 72 ± 8 bpm to 132 ± 14 bpm ($p = 0.0001$, n = 296). Systolic blood pressure increased during dobutamine from 144 ± 24 mmHg to 150 ± 28 mmHg ($p = 0.001$). Diastolic blood pressure decreased from 82 ± 12 mmHg to 76 ± 18 mmHg at the maximum dose of dobutamine ($p = 0.01$).

Age for all subjects as well as for various subgroups are presented in the table as mean ± SD (years), between group comparisons did not reveal statistically significant differences in age.

The $ED_{50\%}$-HR for all subjects as well as for various subgroups are presented in the table. Between group comparisons did not reveal statistically significant differences in dobutamine sensitivity. Subsequently with-in group analysis were

performed on the relationships between age and $ED_{50\%}$-HR. In none of the groups a relationship was found between age and $ED_{50\%}$-HR ($p > 0.05$), with one exception, i.e. the group of "healthy" individuals, in whom an increased sensitivity was noted with advancing age ($p = 0.01$) (figure 1). When divided in 3 groups (40-60 years, n = 20, 61-75 years, n = 20, ≥76 years, n = 14) it appeared that $ED_{50\%}$-HR in the elderly was 13 ± 3% lower than in relatively young. The apparent higher sensitivity of the elderly to dobutamine could be explained by the reduced rise of systolic pressure during dobutamine, so that no baroreflex mediated stimulated vagal activity inhibited the chronotropic response to dobutamine.

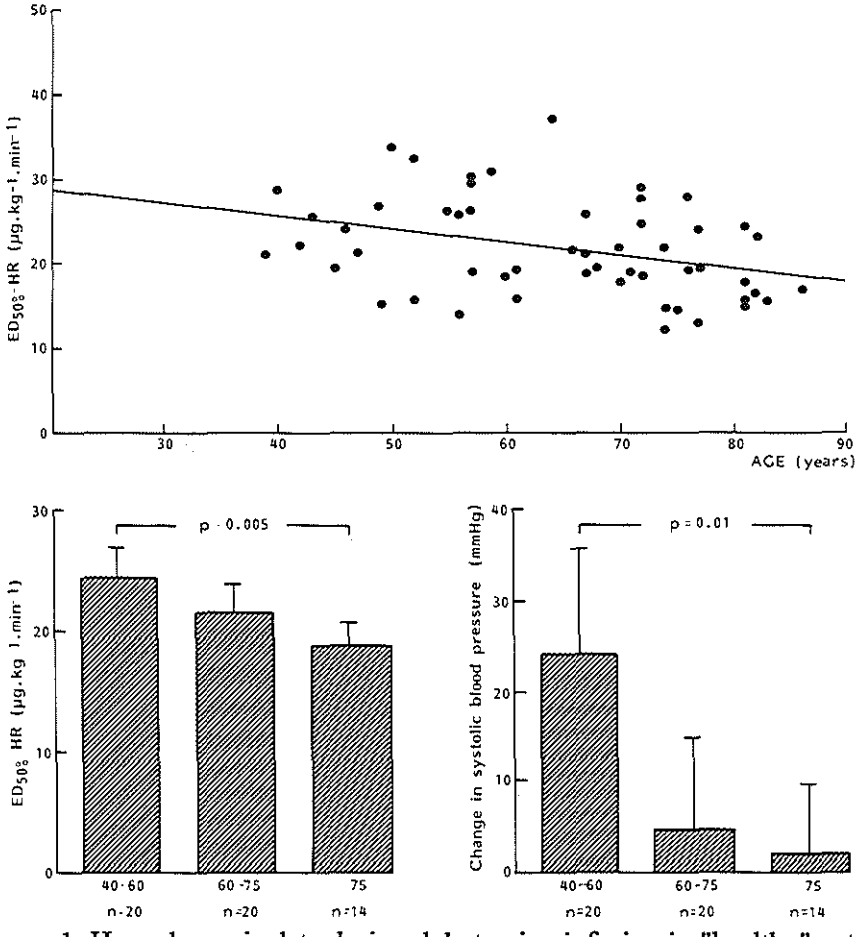

Figure 1 Hemodynamic data during dobutamine infusion in "healthy" patients who have no diabetes, hypertension, smoking, angina and echocardiographic evidence of myocardial ischemia (n = 54). $ED_{50\%}$-HR = dobutamine dose (µgr/kg/min) required to increase heart rate by 50% of the maximum at the highest dose of dobutamine; SBP = change systolic blood pressure (%)

However, a tendency for a reduced sensitivity for dobutamine was noted with an increasing number of parameters for acute ischemia (positive slopes, p-values 0.33, 0.12 and 0.09 respectively in acute ischemia-groups 1,2 and 3). The slope of the relationship between age and $ED_{50\%}$-HR in acute ischemia group 3 was significantly different from "healthy" individuals (+0.13 vs -0.14, p = 0.02). Systolic blood pressure during dobutamine infusion decreased in "healthy" elderly subjects (p = 0.003), in contrast to individuals in "acute ischemia" group 2 and 3 who showed no significant change. Diastolic blood pressure remained unchanged in "healthy" elderly subjects and all individuals in different subgroups. During dobutamine infusion there was a large variation in plasma dobutamine concentration between individual patients. When patients over and under 60 years of age were compared, there was no significant inter-patient difference in the rise of dobutamine plasma concentration during the stress test between these two groups (figure 2).

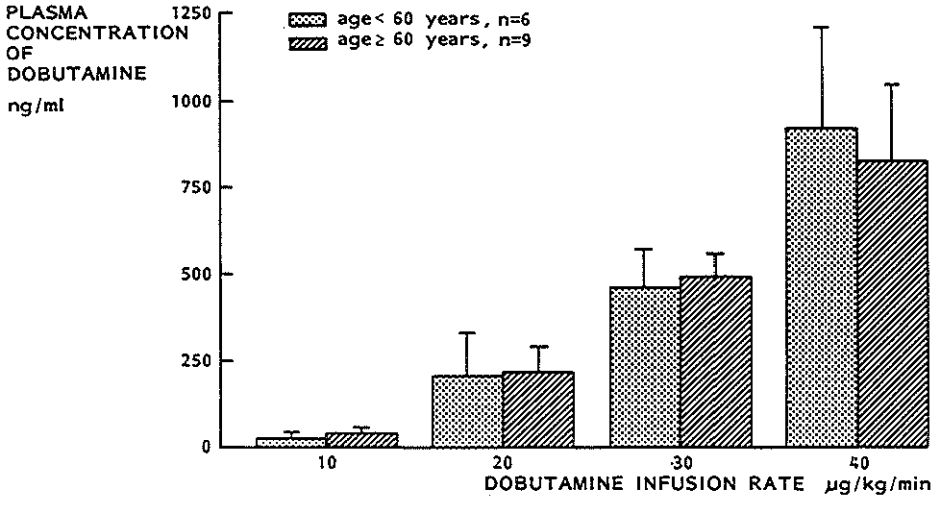

Figure 2 Increase in plasma concentrations of dobutamine during different stages of the test comparing patients over and under 60 years of age. Values are expressed as mean ± SD

Discussion

The effect of ageing on ß-adrenergic receptor mediated responses has been studied mainly by using the chronotropic effect of bolus injections of isoproterenol in rats[7,8]. The "classic" view of reduced cardiac chronotropic responsiveness to ß-adrenoceptor stimulation by isoproterenol was confirmed in humans, where elderly patients were screened for the absence of coronary artery disease by history and physical examination[3,4]. The decreased heart rate

response to isoproterenol in elderly can be caused by a reduced direct chronotropic response or a reduced baroreflex response to vasodilatation occurring during isoproterenol infusion. A study of Docherty et al.[5], using pithed rats, thereby abolishing baroreflex stimulation, showed no difference of isoproterenol induced tachycardia in young and old rats.
In contrast to isoproterenol, dobutamine has little effect on blood pressure, because of its weak stimulation of α_1 and $ß_2$-adrenoreceptors in peripheral blood vessels. The cardiac chronotropic effect of dobutamine is mainly due to $ß_1$-adrenoceptor stimulation[9].

The present study shows in senescent patients no evidence of a reduced ß-adrenoceptor sensitivity to dobutamine. In a sub group of "healthy" elderly patients, i.e. those without diabetes, hypertension, smoking, angina and a normal echocardiography at rest without evidence of ischemia during dobutamine stress, an increased sensitivity for dobutamine induced tachycardia was found. This can be explained by the diminished systolic blood pressure increment in these elderly patients during dobutamine infusion and consequently less baroreflex mediated interference of increased cardiac vagal activity. In patients with acute myocardial ischemia during stress no relationship was found between age and dobutamine sensitivity and blood pressure did not rise during stress. Despite the absent rise in blood pressure this group had a significantly reduced responsiveness to dobutamine as compared to "healthy" patients. Recently Hageman et al.[15] described an attenuated baroreflex sensitivity and reduced efferent cardiac sympathetic activity during experimental acute myocardial ischemia in the dog. In our patients with acute myocardial ischemia induced by dobutamine such a phenomenon could have contributed to their apparent reduced sensitivity to dobutamine.

Pharmacokinetic data on dobutamine in humans are scant. The pharmacokinetic model of dobutamine is that of a first order derivate, indicated by the linear plasma correlation between infusion rate and concentration [16,17]. It should be noted that these studies investigated dobutamine infusions between 2.5 and 10 µg/kg/min, in contrast to the present study which used a maximal dose of 40 µg/kg/min. However, pharmacokinetic changes of dobutamine in the elderly, as a possible explanation for our findings are in our view unlikely, as in a pilot study of 15 patients we found no-age related differences in plasma dobutamine concentrations during infusions.

In conclusion, the sensitivity for dobutamine-induced tachycardia is unchanged in the elderly, also when subgroups with different clinical variables are studied. However, in patients with signs of acute ischemia during dobutamine infusion a reduced sensitivity was found despite an absent rise in systolic blood pressure during dobutamine.

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Table 1 Influence of age on hemodynamic response to infusion of dobutamine

		Age		$ED_{50\%}$-HR		$ED_{50\%}$-HR			SBP			DBP		
	No		p		p	slope	p1	p2	slope	p1	p2	slope	p1	p2
All patients	296	61.3±1.4	NS	21.3	NS	-0.03	0.25	NS	-0.43	0.001	NS	-0.18	0.25	NS
Diabetes	31	62.8±4.8	NS	21.2	NS	+0.03	0.67	NS	+0.13	0.61	NS	-0.07	0.71	NS
Hypertension	100	61.9±2.2	NS	21.6	NS	-0.04	0.46	NS	-0.20	0.11	NS	-0.11	0.44	NS
Smoking	121	63.1±2.2	NS	21.4	NS	0.00	0.90	NS	-0.26	0.04	NS	-0.18	0.15	NS
History of AP	78	59.1±2.6	NS	20.9	NS	-0.07	0.18	NS	-0.55	0.004	NS	-0.39	0.02	NS
History of MI	119	61.3±2.0	NS	21.2	NS	+0.01	0.80	NS	-0.15	0.29	NS	-0.19	0.25	NS
Acute ischemia 1	86	60.0±2.5	NS	21.1	NS	+0.05	0.33	NS	-0.55	0.01	NS	-0.15	0.20	NS
Acute ischemia 2	26	57.4±5.2	NS	22.1	NS	+0.12	0.12	NS	-0.51	0.08	NS	-0.38	0.20	NS
Acute ischemia 3	19	56.4±6.8	NS	21.5	NS	+0.13	0.09	0.02	-0.48	0.11	NS	-0.37	0.27	NS
"Healthy"	54	64.8±3.6		21.8		-0.14	0.01		-0.77	0.003		-0.24	0.18	

No = number of patients; Age = mean age (years) ± SD; p = p value of unpaired t-test of subgroups and "healthy" patients; $ED_{50\%}$-HR = dobutamine dose (µg/kg/min) required to achieve 50% of maximum heart rate; SBP = systolic blood pressure change % during dobutamine infusion; DBP = diastolic blood pressure change % during dobutamine infusion; acute ischemia 1 = presence of new wall motion abnormalities during stress; acute ischemia 2 = presence of new wall motion abnormalities and ECG changes during stress; acute ischemia 3 = presence of new wall motion abnormalities, ECG changes and angina during stress; "Healthy" = absence of smoking, hypertension, diabetes mellitus, previous myocardial infarction and ischemia during stress; p1 = p value of linear regression analysis within one subgroup; p2 = p value of unpaired t-test on slopes of linear regression analysis between subgroups of patients and "healthy" patients; NS = not significant.

CHAPTER 6

DOBUTAMINE STRESS ECHOCARDIOGRAPHY FOR ASSESSMENT OF PERIOPERATIVE CARDIAC RISK IN PATIENTS UNDERGOING MAJOR VASCULAR SURGERY[1]

(Short title: Risk stratification by dobutamine stress test)

Don Poldermans MD, Paolo M Fioretti MD, FESC, Tamas Forster MD, Ian R Thomson MD, Eric Boersma BSE, El-Said M El-Said MB, BCh, MS, Nico AJJ du Bois MD, Jos RTC Roelandt MD, FACC, Hero van Urk MD, FACA.

From the Thoraxcenter and Department of Vascular Surgery, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, The Netherlands.

Abstract

Background. The purpose of the study was to determine the predictive value of dobutamine stress echocardiography for perioperative cardiac events in patients scheduled for elective major non cardiac vascular surgery.
Methods and Results. Patients (n = 136, mean age 68 yrs) unable to exercise underwent a dobutamine stress test preoperatively (incremental dobutamine infusion - 10-40 μg/kg/min, continued with atropine - 0.25-1 mg - i.v., if necessary to achieve 85% of the age predicted maximal heart rate, without symptoms or signs of ischemia). The clinical risk profile was evaluated by Detsky's modification of Goldman's risk factor analysis. Echocardiographic images were evaluated by two observers blinded to the clinical data of the patients, and results of the test were not used for clinical decision making. Technically adequate images were obtained in 134/136 patients, 1 major

[1] Circulation 1993;87:1506-1512

complication occurred (ventricular fibrillation), and 3 tests were discontinued prematurely due to side effects. Finally, data from 131 patients were analyzed with univariate and multivariate methods. The dobutamine stress test was positive (new or worsened wall motion abnormality) in 35/131 pts. In the postoperative period 5 patients died due to myocardial infarction, 9 patients had unstable angina and one patient developed pulmonary edema. All patients with cardiac complications (15 patients) had a positive dobutamine stress test. No cardiac events occurred in patients with negative tests. Five patients with a technically inadequate or prematurely stopped test were operated upon without complications. By multivariate analysis (logistic regression) only age greater than 70 years, and new wall motion abnormalities during the dobutamine test were significant predictors of perioperative cardiac events.
Conclusion. Dobutamine stress echocardiography is a feasible, safe and useful method for identifying patients at high or low risk of perioperative cardiac events. The test yields additional information, beyond that provided by clinical variables, in patients who are scheduled for major non cardiac vascular surgery.

Key-words: dobutamine stress echocardiography - non cardiac vascular surgery - perioperative cardiac risk

Introduction

Perioperative cardiovascular complications such as myocardial infarction, unstable angina, pulmonary edema and serious ventricular arrhythmias, are potentially avoidable causes of mortality and morbidity in surgical patients. Theoretically, if patients with a high risk of cardiac complications can be identified preoperatively, their management can be altered and the chance of an adverse outcome reduced.

This is particularly relevant in candidates for major non-cardiac vascular surgery, who have a relatively high rate of cardiovascular complications. This primarily reflects the high prevalence of coronary artery disease, ranging from 25 to 90% depending upon the patient selection and diagnostic method used[1], in this population.

Several methods have been described for risk stratification in these patients, including multifactorial clinical scoring systems[2,3], ambulatory electrocardiographic monitoring[4], radionuclide ventriculography[5], pharmacological myocardial perfusion imaging[6-28] and angiocardiography[29]. It has been suggested that the most accurate information can be derived by adding clinical data to that obtained by dipyridamole Thallium-201 myocardial perfusion imaging[10]. However, nuclear studies may not be available in all hospitals, and they are relatively expensive. Therefore, a more available and less expensive test would be very desirable. The applicability of stress

echocardiography in this clinical setting is potentially significant. Initial results with dipyridamole and dobutamine stress echocardiography have been promising[27,28,30-34]. However, in the reported series stress echocardiography was performed in relatively small numbers of patients. Accordingly, this study was designed to assess prospectively the predictive value of clinical information and dobutamine stress echocardiography, for identification of individuals at high and low risk of perioperative cardiac complications. A group of consecutive patients undergoing major non cardiac vascular surgery were studied.

Methods

Patient population: 136 consecutive patients (116 male and 20 female) scheduled for elective vascular surgery at the University Hospital Dijkzigt from May 1991 till July 1992 were screened. 51 patients underwent abdominal aortic aneurysm resection, 46 aortobifemoral bypass and 39 infrainguinal arterial reconstruction. Patients undergoing emergency procedure were not enroled. All patients underwent a routine clinical evaluation including a detailed clinical history, physical examination and a 12-lead ECG. Cardiac risk assessment was based on Detsky's modification of Goldman's cardiac risk index[2,3]. Variables used for scoring were: previous myocardial infarction, angina pectoris, left ventricular failure, arrhythmias, age and poor general condition. Detsky scores were calculated for each patient. Risk factors for vascular disease (hypertension, diabetes, smoking) were also analyzed. No patient underwent perfusion stress scintigraphy, coronary angiography or prophylactic myocardial revascularisation prior to surgery.

Dobutamine stress echocardiography: Dobutamine stress echocardiography was performed as previously described[35,36].In short, after giving verbal informed consent, the patients underwent a resting two dimensional precordial echocardiographic examination. Standard apical and parasternal views were recorded on video tape and a baseline 12 lead ECG was recorded. Dobutamine was then administered intravenously by infusion pump, starting at 10 μg/kg/minute for 3 minutes, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/minute (stage 4), and continued for 6 minutes. In patients not achieving 85% of their age-predicted maximal heart rate, who had no symptoms or signs of ischemia, atropine (starting with 0.25 mg increasing to a maximum of 1 mg) was given intravenously at the end of stage 4, while dobutamine was continued. Throughout dobutamine infusion the ECG was continuously monitored, the 12 lead ECG was recorded each minute and blood pressure was measured by sphygmomanometry every 3 minutes. The two dimensional echocardiogram was continuously monitored and recorded on video tape during the final minute of each stage. Metoprolol was available and used to reverse the effects of dobutamine or atropine if these did not revert

spontaneously and quickly. Off-line assessment of echocardiograpic images was performed by 2 experienced investigators without knowledge of the patients' clinical data or perioperative outcome but with knowledge of the doses of dobutamine and atropine used. When there was disagreement between these two assessors, a third investigator viewed the images without knowledge of the previous assessments, and a majority decision was achieved. For this semi-quantitative assessment the left ventricular wall was divided into 14 segments[37] and each was 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, that is a new or worsened wall motion abnormality, constituted a positive test. Absence of a hyperkinetic response to dobutamine was not considered as a positive result. We have previously shown excellent inter and intra observer reproducibility interpretation of stress echocardiography, of 91 and 92%[45] respectively. In addition, the reproducibility of wall motion abnormalities during dobutamine-atropine stress echocardiography was 100% in 23 patients who underwent serial studies on different days[46]. The results of the test were not provided to the attending physicians responsible for clinical management. Therefore, in contrast to most previous studies with dipyridamole thallium scintigraphy, the present study was not limited by a referral bias which could influence the results of the study. The protocol was approved by the hospital ethics committee.

Postoperative follow-up: Patients were followed throughout their stay in hospital. On the 1st, 3rd and 7th postoperative days serum creatine kinase with MB fraction was measured and a 12-lead ECG was recorded. All measurements, such as ECG, cardiac isoenzyme determination and echocardiography were repeated whenever necessary, at the discretion of the treating physicians. Adverse cardiac outcomes included: 1) cardiac death (based on clinical assessment, ECG and if possible autopsy), 2) myocardial infarction documented by ECG and cardiac isoenzymes, 3) unstable angina consisting of chest pain at rest with transient ischemic ECG changes requiring prolonged stay or readmission to the intensive care unit and intravenous treatment with nitrates, 4) sustained ventricular dysrhythmias and 5) pulmonary edema of cardiogenic origin based on clinical assessment and pulmonary artery pressures obtained using a Swan Ganz catheter.

Statistical analysis: Univariate analysis for categorial variables was performed using the chi-square test with Yates correction or Fisher's exact test. Continuous variables were analyzed using Student's t test. Stepwise logistic regression models were fitted to identify independent predictors of a cardiac event (all variables, regardless of significance from the univariate analysis were entered into the multivariate analysis). The difference in risk was expressed as the odds ratio with the corresponding 95% confidence intervals (C.I.). Differences were

considered significant if the null hypothesis could be rejected at the 0.05 probability level.

Results

Patient characteristics: The mean age of the patients was 68 years (range 30-90). There were 116 males and 20 females. Patients with atrial fibrillation and/or left bundle branch block were included in the study although none of the patients had atrial fibrillation at the start of dobutamine infusion. Two patients had a pre-existing history of ventricular arrhythmias, one of whom developed ventricular fibrillation during the test.

A history of arterial hypertension was present in 53 patients, 15 had diabetes mellitus (all on drug therapy) and there were 65 smokers. A history of coronary disease was present in 56 patients (myocardial infarction in 32 patients, angina pectoris in 7 patients and both angina and old infarction in 17 patients). Among those who had no history of coronary disease, one or more risk factors for vascular disease (hypertension, diabetes mellitus or smoking) was reported in 38 patients. When classified according to Detsky's score 1 patient had more than 30 points, 7 patients had 16-30 points and 123 patients had 0-15 points (table 1).

Table 1 Clinical scoring system for cardiac event risk

	Cardiac risk index		
	Cardiac events (N = 15 pts)	No cardiac events (N = 116 pts)	p value
Detsky score	13.2 ± 6.4	6.7 ± 6.0	0.02
Range	0-35	0-30	NS
0-15 Points	13	110	NS
16-30 Points	1	6	NS
>30 Points	1	0	NS

Dobutamine stress test: Technically adequate echocardiographic images were obtained in 134/136 patients during the dobutamine stress test. Two patients were excluded from the study due to uninterpretable image quality. All but 5 patients tolerated the maximum dobutamine dose.

Major side effects occurred in 2 patients. One patient developed ventricular fibrillation during the peak dose of dobutamine, but was successfully resuscitated (one single counter shock) without evidence of new myocardial infarction based on echocardiography, ECG and cardiac isoenzyme determinations. One patient had paroxysmal atrial fibrillation in the recovery

phase of the test, rapidly reverted to sinus rhythm after metoprolol. Three tests were discontinued prematurely due to side effects. Rapidly increasing blood pressure (240/130 mm Hg in stage 1) was the reason for discontinuing the test in one patient with an abdominal aortic aneurysm. In two other patients, the test was stopped because of intolerable chills and shivering. Eight other patients experienced minor side effects which did not prevent completion of the test (headache, tolerable chills, numerous premature ventricular contractions).

Table 2 Univariate analysis of clinical data and stress test results

	Cardiac events (N = 15)	No cardiac events (N = 116)	OR	CI
Age, yrs (range)	70 (50-86)	68 (35-90)		
>70 yrs (No)	9	46	2.3	0.7- 7.8
Sex M/F	11/4	100/16	0.4	0.1- 1.9
History of angina	7	17	5.1	1.4- 18
History of MI	10	39	4.0	1.1- 14
Hypertension	4	49	0.5	0.1- 1.8
Smoking	8	57	1.2	0.4- 3.9
Diabetes	4	11	3.5	0.8- 15
Aortic/infrainguinal surgery	10/5	84/32	0.8	0.2- 2.8
Angina during test	3	10	2.7	0.5- 13
ST changes during test	7	31	2.4	0.7- 8.1
WMA at rest	10	47	2.9	0.9- 11
Severe LV dysfunction at rest	3	14	1.8	0.4- 8.3
NWMA during test	15	20	72	9- 577

OR = odds ratio; CI = 95% confidence interval; WMA = any wall motion at rest; severe left ventricular dysfunction at rest = ≥10 of 14 abnormal left ventricular segments; NWMA = new wall motion abnormalities.

The dobutamine stress test was completed in 131/136 (96%) patients. Addition of atropine to the peak dobutamine dose was required in 39/131 patients. Patients on beta blockers required atropine more often (13/23) than patients not on beta blockers ($p = 0.004$ patients with vs without beta blockers). Metoprolol (1-5 mg) was administered to reverse the adverse effects of dobutamine and/or atropine, such as tachycardia persisting longer than 5 minutes, or ischemia not resolving soon after stopping the dobutamine infusion.

New wall motion abnormalities were detected during the dobutamine stress test in 35 patients, seven of these patients had a normal resting echocardiogram and 28 patients resting wall motion abnormalities. Improvement of existing wall motion abnormalities was observed in 7 patients. Five patients had a left bundle

branch block making interpretation of ST segment changes impossible. ST depression or elevation >1 mm occurred in 34 cases and typical angina in 13 cases. Table 2 summarize the results of dobutamine stress testing.

Postoperative cardiac events: In the postoperative period 15 patients experienced cardiac complications (table 3). All complications occurred between the 1st and 7th postoperative days. Five patients suffered fatal postoperative myocardial infarction, 9 had unstable angina and one developed acute pulmonary edema.

Predictive value of clinical parameters and dobutamine stress test: The clinical features of patients with and without perioperative cardiac events and a complete dobutamine stress test are compared in table 1 and 2. The Detsky score was significantly higher in patients with perioperative complications, but the scoring system was not useful for risk stratification. Thirteen of 15 patients with cardiac events were in the lower risk category (0-15 points). Significant univariate clinical predictors of a cardiac event included a history of angina pectoris (odds ratio 5.1, C.I. 1.4-18), old myocardial infarction (odds ratio 4.0, C.I. 1.1-14.4). Of 5 patients with a fatal myocardial infarction 4 had suffered a previous myocardial infarction. However, risk factors for cardiovascular disease (hypertension, smoking and diabetes mellitus), type of operation procedure (aortic vs. peripheral surgery) and age >70 years were not univariate predictors of perioperative outcome. In contrast to clinical information, dobutamine stress echocardiography was much more useful for risk assessment. All 15 patients with perioperative cardiac events had a positive test (odds ratio 72, C.I. 9.0-557), while the test was positive in only 20 out of 116 patients without events. Other signs of ischemia during the test, such as chest pain and ST segment changes, were not predictive of cardiac events (odds ratio 2.7, C.I. 0.6-11.0 and respectively odds ratio 2.4, C.I. 0.8-7.2).

A multivariate analysis of clinical and dobutamine stress test variables revealed only 2 independent predictors of a cardiac event (table 4). Patients with a positive dobutamine stress test (occurrence of new wall motion abnormalities) were 95 (C.I. 11-823) times more likely to have a perioperative cardiac event. Age >70 yrs was the only clinical parameter (odds ratio 6.0, C.I. 1.28-27.9) independently associated with a greater risk of a perioperative cardiac event. The positive predictive value of dobutamine stress echocardiography was 42% (15/35) and the negative predictive value was 100%.

Discussion

Preoperative cardiac risk stratification of patients undergoing major vascular surgery is a challenge. A combination of clinical evaluation and dipyridamole thallium 201 myocardial scintigraphy has been reported to provide the most useful and efficient prognostic information[10,22]. Recently, numerous publications have appeared regarding the safety, feasibility and diagnostic accuracy of stress echocardiography for eliciting myocardial ischemia both after exercise[36] and pharmacological interventions like dipyridamole and dobutamine administration[30-33,39-42]. These studies indicate that in experienced hands stress echocardiography represents a reasonable alternative[30] in most situations where myocardial perfusion scintigraphy is applied[41].

Our study shows that dobutamine stress echocardiography can also be used prior to major vascular surgery to accurately define a subgroup of patients at high risk of perioperative cardiac complications. Wall motion abnormalities induced by dobutamine were the most important predictors of perioperative cardiac events. In contrast, wall motion abnormalities at rest and other signs and symptoms of ischemia during the test were not predictive.

In addition to detecting deterioration in regional wall motion, echocardiography may also reveal improvement in wall motion during dobutamine infusion. Reversal of existing wall motion abnormality may indicate the presence of hibernating myocardium. Improvement during the test was seen in 7 patients who all had an uneventful perioperative clinical course. Severe left ventricular dysfunction at rest, (defined by echocardiography as ≥10/14 abnormal left ventricular segments), which may warrant specific fluid balance monitoring, was not an independent risk factor for cardiac events.

Clinical data, combined in a risk index such as Detsky's score, provided little information on individual perioperative cardiac risk. Although Detsky's score was significantly higher in the cardiac event group than in the non cardiac event group, there was a large overlap between the patients with and without events.

Table 4 Multivariate analysis of clinical data and dobutamine stress test

	Cardiac events N = 15	No cardiac events N = 116	OR	CI
Age >70yrs	9	46	6.0	1.3 - 28
NWMA during test	15	20	95	11 - 822

OR = odds ratio; CI = 95% confidence interval; NWMA = new wall motion abnormalities.

The presence of coronary artery disease, indicated by typical angina pectoris or old myocardial infarction correlated positively with cardiac events. By multivariate regression analysis the presence of new wall motion abnormalities during dobutamine was the most powerful independent predictor of perioperative events, followed by age >70 years. Risk factors for vascular disease such as smoking, diabetes mellitus and hypertension were not correlated with cardiac events.

There were 2 major side effects during dobutamine stress echocardiography. One patient developed ventricular fibrillation during the peak dose of dobutamine, along with echocardiographic and electrocardiographic evidence of myocardial ischemia. This patient, with a previous myocardial infarction, was successfully resuscitated without evidence of a new infarction. Because of an expanding abdominal aneurysm he was operated one week later without complications.

The other major side effect was paroxysmal atrial fibrillation occurring during the recovery phase of the test, which rapidly responded to metoprolol. The dobutamine stress test has been performed about 500 times in our institution, for various indications including this study with one major complication in the form of ventricular fibrillation. Although the patients number are is still small this represents an event rate of 0.2% which would be comparable to that of dipyridamole thallium scintigraphy[44]. Perhaps the absence of serious side effects in some previous dobutamine stress echocardiographic studies was due to the use of a lower dobutamine dose used and the avoidance of atropine[32,34]. The peak dobutamine dose of 40 μg/kg/min was reached in 118/131 patients and atropine was then added if the target heart rate (expressed as 85% of age predicted maximal heart rate) had not been achieved, and if signs or symptoms of ischemia were absent. Atropine was given in 39/131 patients. We believe the high dose of dobutamine is necessary to provoke adequate myocardial stress and subsequent ischemia. Additional atropine was most frequently required in patients on beta blockers who did not achieve an adequate heart rate response to dobutamine.

The results of the present study are similar to those recently published in a smaller group of 60 patients studied by Lalka et al.[47] with dobutamine stress echocardiography. These authors found a positive predictive value of the test for perioperative events of 29% and a negative predictive value of 95%. The results we obtained by dobutamine stress echocardiography are also similar as those reported by Tischler et al.[26] with dipyridamole echocardiography. They found that a positive test indicated a relative risk of having a cardiac event after vascular surgery of 78 (C.I. 11-564) using the dobutamine stress test we found that a positive test indicated a relative risk of 42 (C.I. 5.7-303). Tischler et al. also found an excellent negative predictive value of dipyridamole echocardiography (only one event among 100 patients with a negative test). The similar prognostic information provided by dobutamine and dipyridamole stress

echocardiography is also consistent with recent studies indicating that the value of the two tests is very similar for the diagnosis of coronary disease, despite their different mechanism of action[31,40].

Our data and those of Tischler[26] suggest that pharmacological stress echocardiography may be an alternative to nuclear studies for preoperative risk stratification. Compared to nuclear studies stress echocardiography is likely to be less expensive in many hospitals, as long as the number of technically inadequate studies is low. In our hospital dipyridamole thallium scintigraphy costs about US $531 compared to about US $ 185 for dobutamine stress echocardiography.

The positive predictive value of a positive dobutamine stress echocardiography is at least comparable to dipyridamole thallium scintigraphy (42% vs 30%) when data obtained from 15 studies are used for comparison[7-21]. These studies were published from 1985 to 1991 and contain the results of 1204 patients tested preoperatively by dipyridamole thallium 201 myocardial perfusion scintigraphy. There are several possible explanations for the high sensitivity of dobutamine stress echocardiography in our study. Firstly, the results of the test were not provided to the attending physicians and did not influence clinical management. Secondly, the patients studied had a high prevalence of documented coronary artery disease (41%). Finally, thallium scintigraphy detects both myocardial ischemia and maldistribution of flow while stress echocardiography has a high specificity for myocardial ischemia[43].
One potential limitation of the present and of other similar studies is the subjective non quantitative interpretation of echocardiographic images. However this was always done by 2 investigators blinded to the clinical information and the outcome of surgery.

In summary, our study shows that dobutamine stress echocardiography is an extremely promising new tool for risk stratification in patients who are candidates for major vascular surgery and may be an alternative to nuclear myocardial perfusion studies.

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Table 3 Clinical data on patients with perioperative cardiac events

Preoperative clinical data										DSE			days	
Pt	Age	HTN	DM	Smok	AP	MI	Detsky	ECG	Med	NWMA	CHP	ST	Event	Time
1	70	no	no	yes	no	yes	10	inf MI	no	yes	yes	yes	FMI	3
2	76	no	no	no	no	yes	10	ant MI	no	yes	no	yes	FMI	5
3	76	no	no	yes	yes	yes	15	ant MI	no	yes	no	no	FMI	5
4	62	yes	yes	no	no	no	0	norm	yes	yes	no	yes	FMI	3
5	85	no	no	no	no	yes	10	ant MI	no	yes	no	no	FMI	7
6	83	yes	no	yes	no	no	5	RBBB	yes	yes	no	yes	UAP	1
7	50	yes	yes	no	yes	yes	10	LVH	yes	yes	yes	yes	UAP	1
8	72	no	yes	no	yes	yes	25	inf MI	yes	yes	no	no	UAP	1
9	76	no	no	yes	yes	yes	15	inf MI	yes	yes	yes	yes	UAP	1
10	76	no	no	yes	no	no	15	norm	no	yes	no	no	UAP	1
11	73	yes	no	no	yes	no	15	norm	no	yes	no	no	UAP	5
12	77	yes	no	no	yes	no	15	inf MI	yes	yes	no	no	UAP	1

13	51	no	no	no	yes	yes	35	inf MI	yes	yes	yes	yes	UAP	2
14	72	no	no	yes	yes	yes	25	ant MI	yes	yes	no	yes	UAP	3
15	66	yes	no	yes	no	yes	5	norm	yes	yes	no	no	Pul Edema	2

DSE = dobutamine-atropine stress echocardiography; Pt = patient; HTN = hypertension; DM = diabetes mellitus; Smok = smoking; AP = history of angina pectoris; MI = history of myocardial infarction; Detsky = detsky's score; RBBB = right bundle branch block; norm = normal; LVH = left ventricular hypertrophy; Med = antianginal medication; NWMA = new wall motion abnormalities; CHP = chest pain during test; ST = ST-segment changes, >1 mm during stress echocardiography; Event = perioperative event; FMI = fatal myocardial infarction; UAP = unstable angina pectoris; Pul Ed = pulmonary edema.

CHAPTER 7

DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHY FOR ASSESSMENT OF PERIOPERATIVE AND LATE CARDIAC RISK IN PATIENTS UNDERGOING MAJOR VASCULAR SURGERY[1]

(Short title: Risk stratification and prognostic information of dobutamine-atropine stress test)

Don Poldermans MD*, Paolo M Fioretti MD, PhD, Tamas Forster MD, PhD, Eric Boersma BSE, Mariarosaria Arnese MD, Nico AJJ du Bois MD*, Jos RTC Roelandt MD, PhD, Hero van Urk MD, PhD*.

From the Department of Vascular Surgery* and the Thoraxcenter, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, the Netherlands.

Abstract

Objective: To determine the value of dobutamine-atropine stress echocardiography and clinical variables to predict perioperative and late cardiac events in patients scheduled for elective major noncardiac vascular surgery.
Design: Blinded prospective study.
Patients: Patients (n = 187 mean age 69 yrs).
Measurements: Dobutamine-atropine stress test was performed preoperatively. Results were not used for clinical management. The clinical risk profile was evaluated by Detsky's score.
Results: Technically adequate images were obtained in 185/187 patients, 1 major complication occurred (ventricular fibrillation) and 4 tests were prematurely stopped due to side effects. Data from 181 patients were analyzed. The stress test was positive (new or worsened wall motion abnormality) in

[1] Eur J Vasc Surg, accepted for publication

56/181 patients. Perioperative cardiac events were: 5 fatal myocardial infarctions, 3 nonfatal myocardial infarctions, 9 unstable angina pectoris and 1 pulmonary edema. All patients with a cardiac event had a positive stress test (18/56). No event occurred in patients with a negative stress test. By multivariate analysis only a new wall motion abnormality during the stress test (odds ratio 45.0, 6-369) was a significant predictor of cardiac events.

Patients (n = 154) were followed after operation for 16 ± 9 months. Twenty-four cardiac events occurred in 21 patients: 6 fatal myocardial infarctions, 3 nonfatal myocardial infarctions, 6 unstable angina pectoris, 3 ventricular arrhythmias and 6 congestive heart failures. The stress echo was positive in 19/21 patients with late cardiac events. The cardiac events correlated by multivariate analysis with a history of myocardial infarction (odds ratio 9.6, 1.9-47.7) and new wall motion abnormalities (odds ratio 6.2, 1.5-25.1).

Conclusion: Dobutamine-atropine stress echocardiography is a relatively safe and useful test to identify patients at risk of perioperative and late postoperative cardiac events.

Introduction

Coronary artery disease is often present even in asymptomatic patients scheduled for major noncardiac vascular surgery and is the predominant factor for early and late morbidity and mortality after surgery [1,2,3]. Preoperative cardiac evaluation aims at improvement of short and perhaps even long-term outcome by the identification of a group at high cardiac risk. This might select patients who are candidates for coronary revascularisation before surgery, or who would undergo a less extensive operation, receive additional perioperative medication (i.e. nitrates and/or beta blockers) and/or more intensive postoperative monitoring.

The best information for the treating physician would be obtained by a test that identifies high cardiac risk patients before operation and provides prognostic information for late cardiac events after surgery as well. Preoperative cardiac risk stratification in patients undergoing major noncardiac surgery is difficult. Many patients are incapable of performing adequate physical exercise for noncardiac reasons. This explains the relatively low specificity of clinical risk profiles such as the Goldman classification and Detsky score[4,5]. Numerous methods are available to assess objectively the extent of coronary artery disease. These include: ambulatory ECG monitoring[6], radionuclide ventriculography[7], pharmacological myocardial perfusion imaging[8-11], and angiocardiography[2]. At this moment the most efficient and accurate information can be derived by adding clinical data to those obtained by dipyridamole ^{201}Tl myocardial perfusion imaging[8]. Dipyridamole ^{201}Tl myocardial scanning provides

information regarding myocardial ischemia and left ventricular function as well[11].

Stress echocardiography is a relatively new tool[12-17]. Dobutamine stress increases myocardial oxygen demand because of its positive chronotropic and inotropic effects. The addition of atropine potentiates the test, especially in patients with beta-blocker medication without increasing side effects[18]. Dobutamine-atropine stress echocardiography is an attractive alternative for risk stratification methods as it is 1) widely available, 2) relatively cheap and 3) combines information on left ventricular function at rest (an important marker for long-term survival)[19] with detection of areas of ischemic myocardium (also correlated with perioperative cardiac events)[20]. Our study is an extension of a previous investigation[21] which prospectively assessed the predictive value of dobutamine-atropine stress echocardiography for perioperative cardiac events. This study is based on a larger cohort of patients and aims not only to reevaluate the dobutamine-atropine stress echo for predicting perioperative events but also to assess whether the test provides prognostic information for late cardiac events after surgery in these patients.

Methods

Patient population: One hundred eighty-seven consecutive patients (158 men and 29 women) scheduled for elective major noncardiac vascular surgery at the University Hospital Dijkzigt-Rotterdam from May 1991 to January 1993 were screened. Sixty-five patients underwent abdominal aortic aneurysm resection, 65 aortobifemoral bypass, and 57 infrainguinal arterial reconstruction. All patients underwent a routine clinical evaluation, including a detailed clinical history, a physical examination, and a 12-lead ECG. Cardiac risk assessment was based on Detsky's[5] modification of Goldman's cardiac risk index. Variables used for scoring were: age >70 years, previous myocardial infarction, angina pectoris, poor general condition, congestive heart failure and cardiac arrhythmias. Detsky's score was calculated for each patient. Risk factors for vascular disease (smoking, hypertension and diabetes mellitus) were also analyzed. In only 3 patients had a preoperative dipyridamole thallium scintigraphy already been done by the referring physician (which provided no additional information). No patient underwent perfusion stress scintigraphy, coronary angiography or prophylactic myocardial revascularisation before operation.

Procedure and design: Dobutamine-atropine stress echocardiography: Dobutamine-atropine stress echocardiography was performed as previously described[22]: after giving verbal informed consent, the patients underwent a resting two-dimensional precordial echocardiographic examination. Standard

apical and parasternal views were recorded on video tape. A baseline 12-lead ECG was recorded. Dobutamine was then administrated intravenously by infusion pump, starting at 10 μg/kg/min for 3 minutes, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min (stage 4), and continued for 6 minutes. In patients who did not achieve 85% of their age-predicted maximal heart rate and who had no symptoms or signs of ischemia, atropine (starting with 0.25 mg and increasing to a maximum of 1 mg) was given intravenously at the end of stage 4, while dobutamine was continued. Throughout dobutamine infusion, the ECG was continuously monitored, a 12-lead ECG was recorded at the end of each minute in the left lateral decubitus position. Chest electrodes were sometimes slightly shifted in order to get the best echographic window and their position was not changed during the test. Blood pressure was measured by sphygmomanometry every 3 minutes. The two-dimensional echocardiogram was continuously monitored and during later examinations displayed on a quad screen format and recorded on videotape during the final minute of each stage. Metoprolol and atropine were available and were used to reverse the effects of dobutamine or atropine if these did not revert spontaneously and quickly. Indications for terminating the test were: obvious new wall motion abnormalities by echo, ST depression >2 mm at 80 ms after the J point, ST elevation >2 mm, significant chest pain, reduction in systolic blood pressure >40 mmHg from that at rest, or any serious side effects regarded as being due to dobutamine or dobutamine combined with atropine. Off-line assessment of echocardiographic images was performed by two experienced investigators without knowledge of patients' clinical data or perioperative outcome but with knowledge of the doses of dobutamine and atropine used. When there was a disagreement between these two 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 14 segments[23] and each was scored on a four point scale: 1, normal; 2, hypokinetic; 3,akinetic; and 4, dyskinetic. An increase in score between rest and stress in one or more segments, that is, new or worsened wall motion abnormality, constituted a positive test. A lack of improvement of wall motion during dobutamine was not considered a positive result. The results of the test were not provided to the attending physicians responsible for clinical management, so our study was not influenced by a referral bias. The protocol was approved by the hospital ethics committee.

Perioperative follow up: After surgery patients were followed by one physician unaware of dobutamine-atropine stress test results until hospital discharge. A 12 lead ECG and cardiac isoenzymes determination was done on day 1,3 and 7. All measurements, such as ECG, cardiac isoenzyme determination and echocardiography were repeated whenever necessary, at the discretion of the treating physicians. Cardiac events were classified as: 1) cardiac death (based

on clinical assessment, ECG, and if possible, autopsy); 2) myocardial infarction documented by symptoms ECG and cardiac isoenzymes; 3) unstable angina pectoris consisting of chest pain at rest with transient ECG changes requiring readmission or prolonged stay at the intensive care unit and intravenous therapy with nitrates; 4) sustained ventricular dysrhythmias; and 5) pulmonary edema of cardiogenic origin based on clinical assessment and pulmonary artery pressures obtained by Swan-Ganz catheter.

Long-term follow up: Most patients were followed at the outpatient clinic of the Dijkzigt University Hospital. The following events were ascertained: 1) cardiac death; 2) myocardial infarction; 3) unstable angina pectoris; 4) coronary artery bypass surgery or percutaneous transluminal angioplasty; 5) congestive heart failure; 6) noncardiac death; 7) stroke. If two or more events occurred in the same patient both events were counted. The information was obtained by visit at the outpatient clinic, readmission to the hospital, or written contact with the referring physician. All hospital readmissions were investigated by review of procedures and discharge diagnoses from the hospital record.

Statistical analysis: Univariate analysis for categorial variables was performed with the X^2 test with Yates' correction or Fisher's exact test. Continuous variables were analyzed by Student's *t* test. Stepwise logistic regression models were fitted to identify independent predictors of a cardiac event (all variables, regardless of significance from the univariate analysis, were entered into the multivariate analysis). The difference in risk was expressed as the odds ratio with the corresponding 95% confidence intervals (C.I.). Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

Results

Patient characteristics: the mean age was 69 years (range 30-90 years). There were 158 men and 29 women. There were no contraindications for entering the study. Two patients had atrial fibrillation at rest. The ECG was normal in 99 patients, a left bundle branch block was found in 5, a right bundle branch block in 10, left ventricular hypertrophy in 14 and an old myocardial infarction in 63. Two patients had a preexisting history of ventricular arrhythmias, one of whom developed ventricular fibrillation during the test. Hypertension was present in 78 patients, diabetes mellitus in 22 patients and smoking in 90 patients. A history of coronary artery disease was documented in 69 patients (myocardial infarction in 38 patients, angina pectoris in 9 patients, and both angina and old infarction in 22 patients). When classified according to Detsky's score, one patient had >30 points, 11 patients had 16-30 points, and 175 patients had 0-15 points.

Dobutamine-atropine stress test: In 185/187 examinations adequate echo images could be obtained during dobutamine-atropine stress test. Two patients were excluded from the study, both had severe chronic pulmonary disease. All but six patients tolerated the maximum dose of dobutamine. Major side effects occurred in two patients. One patient developed ventricular fibrillation, was successful resuscitated with one counter shock without a new myocardial infarction another patient developed paroxysmal atrial fibrillation in the recovery phase of the test, which rapidly reverted to sinus rhythm after metoprolol. Four tests were stopped because of side effects. Rapidly increasing blood pressure (240/130 mmHg in stage 1) was the reason for stopping the test in one patient with an abdominal aneurysm. In two other patients the test was stopped because of intolerable chills and shivering. One patient experienced bradycardia and hypotension, with a decrease of systolic blood pressure of >40 mmHg, reversed by atropine and tilting of the legs. In the last patient echocardiographically detected myocardial ischemia was present in the inferior part of the left ventricle. Forty patients experienced minor side effects which did not prevent completion of the test: hypotension (decrease of systolic blood pressure compared to base line value >20, <40 mmHg) in eight patients; hypertension (systolic blood pressure >220 mmHg) in eight patients, chills in four patients; numerous premature ventricular contractions in seventeen patients and headache in three patients.

The dobutamine-atropine stress test was completed in 181/185 patients (97%). Addition of atropine to peak dobutamine dose was given in 47 of 181 patients. Patients on ß-blockers required atropine more often than patients not on ß-blockers ($p = 0.004$, patients with versus without ß-blockers). Metoprolol (1-5 mg) was administered to reverse the side effects of dobutamine and/or atropine, such as tachycardia persisting longer than 5 minutes or ischemia not resolving quickly after the stress test was stopped.

New wall motion abnormalities during dobutamine-atropine stress test were detected in 56 patients; of these 41 had a normal resting echocardiogram, 15 patients developed a worsening of an existing wall motion abnormality. ST segment depression or elevation >1 mm occurred in 49 examinations and typical angina in 14 examinations.

Perioperative cardiac events: perioperative events were those cardiac events occurring in the first 30 days after surgery. Eighteen patients experienced perioperative cardiac complications. All cardiac complications occurred in the first seven days after surgery. Five patients suffered a fatal myocardial infarction, three a nonfatal myocardial infarction, nine unstable angina pectoris, and one developed acute pulmonary edema (table 2).

Late cardiac events: all events occurring 30 days after surgery were considered late events. Follow up data were obtained over a 16 ± 9 month (range 4 to 24)

period excluding patients who died in the perioperative period. No patients were lost to follow-up. Nineteen patients experienced 24 cardiac events. Six patients suffered a cardiac death, three a non fatal myocardial infarction, six unstable angina pectoris, three ventricular arrhythmias and six cases of severe congestive heart failure (two patients underwent coronary angioplasty). Six patients had a stroke and three patients suffered noncardiac deaths (one esophageal cancer and two infected protheses).

Predictive value of clinical variables and dobutamine-atropine stress test

Perioperative cardiac events: Univariate analysis of clinical variables and dobutamine-atropine stress test results of patients who completed the stress test are compared in tables 3 and 4. When clinical variables are grouped together in Detsky's score, patients with perioperative cardiac events have a significantly higher score than patients without events (14.4 ± 8.2 vs 6.5 ± 5.4). The large overlap of the data prevented this score from being useful for individual patient cardiac risk stratification (table 1).

Table 1 Clinical scoring system for risk of perioperative cardiac event

	Cardiac events N = 18	No cardiac events N = 163	p value
Detsky score	14.4 ± 8.2	6.5 ± 5.4	<0.002
Range	0 - 35	0 - 30	NS
0-15 points	14	154	NS
16-30 points	3	9	NS
>30 points	1	0	NS

NS = not significant.

Table 3 Univariate analysis of clinical data and perioperative cardiac events (N = 181)

	odds ratio	95% C.I.
Diabetes mellitus	3.7	1.0-14
History of myocardial infarction	3.6	1.1-12
History of angina	3.2	0.9-11
Age >70 years	1.5	0.5-4.7
History of congestive heart failure	1.3	0.2-10
Smoking	1.0	0.3-3.1
Hypertension	0.6	0.2-2.0

95% C.I. = 95% confidence interval.

Table 4 Univariate analysis of stress test results and perioperative events (N = 181)

	odds ratio	95% C.I.
New wall motion abnormalities	48	6.3-1000
Rest wall motion abnormalities	3.5	1.1- 12
Angina during test	2.9	0.6- 13
ST segment changes	2.8	0.9- 9.2

95% C.I. = 95% confidence interval.

Significant univariate clinical variables for predicting perioperative cardiac events were: 1) diabetes mellitus (odds ratio 3.7, 1.0-13.7) and 2) previous myocardial infarction (odds ratio 3.6, 1.1-12.7). Of eight patients who suffered a perioperative myocardial infarction seven had a previous myocardial infarction. All other clinical variables such as: age ≥70 years, history of angina pectoris, smoking, hypertension and type of operation (aortic versus peripheral surgery) were not predictive of perioperative cardiac events.

Univariate analysis of echocardiographic stress test results were highly predictive for perioperative cardiac events, new wall motion abnormalities (odds ratio 48, 6.3-1000) and diffuse echocardiographic rest wall motion abnormalities (asynergy in 5/14 segments) (odds ratio 3.5, 1.1-12.4). Other signs and symptoms of ischemia during stress test were not predictive for perioperative cardiac events, angina pectoris (odds ratio 2.9, 0.6-13) and ST segment changes (odds ratio 2.8, 0.9-9.2). The addition of atropine to complete the stress test was not related to perioperative cardiac events (odds ratio 1.3, 0.4-4.4).

Predictive variables by multivariate analysis of stress test results are presented in table 5. Patients with new wall motion abnormalities had the highest chance of perioperative cardiac events (odds ratio 45, 6-369). All other clinical variables and stress test results were not predictive.

Table 5 Multivariate regression analysis of stress test results for prediction of perioperative cardiac events (N = 181)

	odds ratio	95% CI
new wall motion abnormalities	45.0	6-369

95% C.I.= 95% confidence interval.

Late cardiac events: twenty-four cardiac events occurred in twenty-one patients, of which 19/21 patients had a positive test. By univariate analysis clinical data predictive for late cardiac events were the following: 1) history of myocardial infarction (odds ratio 14.3, 2.9-96), 2) history of congestive heart failure (odds

ratio 7.9, 1.3-45) and 3) history of angina pectoris (odds ratio 5.8, 1.6-20) (table 6) Stress test results which were highly predictive for late cardiac events were: 1) new wall motion abnormalities (odds ratio 17, 3.4-115), 2) diffuse echocardiographic rest wall motion abnormalities (abnormalities ≥5/14 segments) (odds ratio 6.0, 1.5-28).

Table 6 Univariate analysis of clinical data and cardiac events during long-term follow up (N = 154)

	odds ratio	95% C.I.
History of myocardial infarction	14.3	2.9-96
History of congestive heart failure	7.9	1.3-45
History of angina pectoris	5.8	1.6-20
Diabetes mellitus	1.1	0.3-4.3
Hypertension	1.0	0.3-3.5
Smoking	1.0	0.3-3.3
Age >70 years	0.6	0.1-2.0

Other signs and symptoms of ischemia during the test, such as angina pectoris and ST segment changes, were not predictive of late cardiac events (table 7). However multivariate regression analysis showed a positive predictive value of a previous myocardial infarction (odds ratio 9.6, 1.9-47.7) and new wall motion abnormalities (odds ratio 6.2, 1.5-25.1) (table 8).

Table 7 Univariate analysis of stress test results and cardiac events during long-term follow up (N = 154)

	odds ratio	95% C.I.
New wall motion abnormalities	17	3.4-115
Rest wall motion abnormalities	6.0	1.5-28
Angina during test	3.4	0.7-7.8
ST segment changes	1.5	0.4-5.2

95% C.I. = 95% confidence interval.

Table 8 Multivariate regression analysis of clinical data and stress test results for prediction of long-term cardiac events after surgery. Follow up 16 ± 9 months (N = 154)

	odds ratio	95% C.I.
Previous myocardial infarction	9.6	1.9-47.7
New wall motion abnormalities	6.2	1.5-25.1

95% C.I. = 95% confidence interval.

Discussion

Preoperative cardiac risk stratification for patients undergoing major noncardiac vascular surgery is difficult. Many patients have extensive coronary artery disease which may be dormant due to lack of exercise capacity for noncardiac reasons. The development of more objective tests for coronary artery disease has not overcome this difficulty. Exercise ECG is of limited value in presence of resting ECG changes which preclude reliable ST segment analysis during exercise and it is often also limited due to insufficient exercise capacity of these patients[3]. Tests not dependent on physical exercise are the best alternative. Dipyridamole thallium-201 scintigraphy combined with clinical data provides the best information for perioperative cardiac events. Late cardiac events, more often associated with diminished left ventricular function, can be predicted if a low heart:lung thallium-201 ratio is present[11]. This would be helpful for the treating physician, providing not only information about perioperative risk, but also offering long-term prognostic information.

This study shows dobutamine-atropine is a reliable and feasible alternative to nuclear scanning. It required termination before test end point in only 3 percent (4/185). By univariate analysis perioperative cardiac complications are highly correlated with a positive test, the relative risk of a cardiac event is 48, while clinical markers such as a previous myocardial infarction (odds ratio 3.6, 1.1-12.7) and diabetes mellitus (odds ratio 3.7, 1.0-13) are far less predictive. In the late postoperative period univariate analysis shows new wall motion abnormalities to be less predictive for cardiac events, the relative risk is 6.2, but markers of reduced left ventricular function become more important, with a relative risk of 6 vs 3.5 for perioperative events. By multivariate regression analysis perioperative cardiac events are only predicted by new wall motion abnormalities with a sensitivity of the test of 100% but a specificity of only 77%. Cardiac events during long-term follow-up were correlated by multivariate regression analysis with a previous myocardial infarction (odds ratio 9.6, 1.9-47.7) and with new wall motion abnormalities (odds ratio 6.2, 1.5-25.1). The predictive value of new wall motion abnormalities was less for late cardiac events compared to perioperative ones. Myocardial ischemia is not a powerful predictor for long-term events, while diffuse rest wall motion abnormalities are correlated with late events only by univariate analysis, but not by multivariate analysis. This may be due to the population studied or the length of follow up.

In our previous study[21] seniority ($\geq$70) was also an independent predictor of perioperative events, but as the study population expanded this finding was lost. The major limitation of this study remains the subjective interpretation of echocardiographic results, although we have shown excellent interobserver and intraobserver results in previous studies[24,25].

The ultimate question remains of how patients scheduled for major vascular surgery should be evaluated and managed[26]. The combination of clinical data

and dobutamine-atropine stress test is capable of selecting patients with high perioperative cardiac risk and provides information for long-term cardiac events after surgery as well. Preoperative coronary artery revascularisation has long been believed to be the method of choice as concluded by Hertzer et al.[2]. We do not share this opinion. Our average patient age is older and the sex distribution is different compared to the study population of Hertzer. This should imply a higher operative mortality than his but was not confirmed by our perioperative mortality rate of 2.7 percent.

The best option in our view would be first to identify patients at high risk by a dobutamine-atropine stress echo and protect these patients perioperatively with ultra-short acting beta blockers, such as esmolol, and keep these patients in the intensive care unit longer since all our cardiac complications occur in the first seven days after surgery. After surgery cardiac complaints can be treated with medication, coronary angioplasty or coronary surgery. This more restrictive approach to the large number of patients referred for major noncardiac surgery would reduce cost and delay and limit coronary artery interventional procedures to those with conventional indications.

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Table 2 Clinical data on patients with perioperative events

Preoperative clinical data										DASE				
pat	age	HTN	DM	smoking	AP	MI	Detsky	ECG	med	NWMA	CHP	ST	event	time
1	70	-	-	+	-	+	10	Inf MI	-	+	+	+	Fatal MI	3
2	76	-	-	-	-	+	10	Ant MI	-	+	-	+	Fatal MI	5
3	76	-	-	+	+	+	15	Ant MI	-	+	-	-	Fatal MI	5
4	62	+	+	-	-	-	0	Normal	+	+	-	+	Fatal MI	3
5	85	-	-	-	-	+	10	Ant MI	-	+	-	-	Fatal MI	7
6	55	-	+	+	-	+	15	Inf MI	-	+	-	-	Non fatal MI	1
7	53	+	+	+	+	+	20	Ant MI	+	+	+	+	Non fatal MI	4

8	69	+	-	-	+	+	15	Inf MI	+	+	-	-	Non fatal MI	4
9	83	+	-	+	-	-	5	RBBB	+	+	-	+	UAP	1
10	50	+	-	-	+	+	10	LVH	+	+	+	+	UAP	1
11	72	-	+	-	+	+	25	Inf MI	+	+	-	-	UAP	1
12	76	-	+	+	+	+	15	Inf MI	+	+	+	+	UAP	1
13	76	-	-	+	-	-	15	Nor mal	-	+	-	-	UAP	1
14	73	+	-	-	+	-	15	Nor mal	-	+	-	-	UAP	5
15	77	+	-	-	+	-	15	Inf MI	+	+	-	-	UAP	1
16	51	-	-	-	+	+	35	Inf MI	+	+	+	+	UAP	2
17	72	-	-	+	+	+	25	Ant MI	+	+	-	+	UAP	3

Preoperative clinical data										DASE				
pat	age	HTN	DM	smoking	AP	MI	Detsky	ECG	med	NWMA	CHP	ST	event	time
18	66	+	-	+	-	+	5	Normal	+	+	-	-	Pulmonary edema	2

DASE, dobutamine-atropine stress echocardiography; Age, years of age; HTN, hypertension; DM, diabetes mellitus; AP, history of angina pectoris, MI, history of myocardial infarction; Detsky, Detsky's score;
Med, antianginal medication; NWMA, new or worsened wall motion abnormality; CHP, chest pain during stress echo; ST, ST changes >1mm during stress echocardiography; -, negative, +, positive; inf, inferior;
ant, anterior; RBBB, right bundle branch block; LVH, left ventricular hypertrophy; UAP, unstable angina pectoris.

CHAPTER 8

HEMODYNAMICS, SAFETY AND PROGNOSTIC VALUE OF DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHY IN 177 ELDERLY PATIENTS UNABLE TO PERFORM AN EXERCISE TEST[1]

(Short title: Dobutamine-atropine stress echocardiography in elderly patients)

Don Poldermans*, MD, Paolo M Fioretti, MD, FESC, Eric Boersma, BSE, Ian R. Thomson, MD, Mariarosaria Arnese, MD, Hero van Urk*, MD, Jos RTC Roelandt, MD, FACC

From the Thoraxcenter and Department of Vascular Surgery*, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, the Netherlands.

Abstract

Objective: To establish hemodynamic effects, safety and prognostic value of dobutamine-atropine stress echocardiography in patients ≥70 years.
Design: Prospective study.
Setting: University Hospital.
Patients: 179 patients, (mean age 75 years, range 70-90), referred for chest pain (73) or preoperative risk assessment for major vascular noncardiac surgery (106).
Measurements: All patients underwent clinical evaluation and dobutamine-atropine stress test, test results were not used for clinical management.
Results: 179 examinations were performed, 47 included atropine addition. In two examinations no adequate echo images could be obtained and were excluded from the study. Target heart rate (85% of theoretical maximal heart

[1] Arch Int Med, accepted for publication

rate) as test end-point was reached in 165 (93%) examinations. New wall motion abnormalities as a marker of myocardial ischemia occurred in 50 (28%) examinations, ST segment changes in 45 (25%) and angina pectoris in 33 (18%). Reasons for prematurely stopping the test (12): 5 (2.7%) severe chest pain, 1 (0.6%) electrocardiographic changes, 2 (1.1%) hypotension, 2 (1.1%) chills and 2 (1.1%) cardiac arrhythmias (paroxysmal atrial fibrillation). No death or myocardial infarction occurred.

Perioperative events occurred in 12 (4 cardiac death, 3 infarctions, 5 unstable angina). During 16 ± 6 months follow up of 166 patients, 22 cardiac events occurred (8 cardiac death, 4 infarctions, 10 unstable angina pectoris). Perioperative cardiac and late cardiac events were correlated by multivariate regression analysis only with new wall motion abnormalities during stress respectively (odds ratio 51, 5.8-454) and (odds ratio 5.2, 2.0-14).

Conclusion: dobutamine-atropine stress echocardiography is a feasible and safe test for assessing elderly patients with suspected and/or proven coronary artery disease, providing useful prognostic information for perioperative and late cardiac risk, with relatively few side effects.

Introduction

The proportion of people over 60 years of age in Europe will probably increase to over 60% by 2025[1]. This will be reflected strongly by the increasing age of patients admitted to our hospitals. A large number of these patients will have atherosclerotic diseases such as coronary artery disease, peripheral arterial disease, aortic aneurysms and stroke. The treatment of most diseases (including non-cardiac disorders) will partly depend on the cardiac status of these patients. For instance, patients with peripheral vascular disease and high perioperative cardiac risk might be scheduled for a less extensive operation or transluminal angioplasty. Clinical cardiac evaluation of the elderly is limited by decreased exercise capacity, mostly due to noncardiac factors. This explains the great potential clinical relevance of pharmacological stress tests in these patients, which are independent of exercise capacity[2,3,4,5,6].

The most widely used for pharmacological stress agents are dipyridamole and dobutamine, sometimes combined with atropine[7,8]. Dipyridamole induces myocardial ischemia by coronary vasodilatation and increased cardiac output due to systemic vasodilatation, with subsequent ischemia in areas with critical stenosis. Dobutamine increases myocardial oxygen demand by positive chronotropic and inotropic effects on the heart, closely resembling physical exercise[9,10]. Dobutamine stress combined with echocardiography was recently proposed for the diagnosis of coronary artery disease by detection of ischemia-induced wall motion abnormalities[11-14]. The test is inexpensive, potentially widely available and provides diagnostic and prognostic information in the

general patient population[5]. A possible disadvantage for elderly patients may be a diminished chronotropic response to catecholamines[16,17].

This study provides specific information on safety, hemodynamics, and prognostic information for perioperative and late cardiac events of dobutamine-atropine stress test in septua- and octogenarians.

Methods

Patient characteristics: 179 examinations were attempted in patients older then 69 years (129 men, mean age 75 range 70 to 90 years) with known or suspected coronary artery disease from December 1990 till July 1993. Indications for examination were: evaluation of chest pain in 73 and preoperative cardiac risk stratification before non-cardiac vascular surgery in 106[18]. Test results were not used for clinical management. A history of previous myocardial infarction was present in 76 cases, typical angina pectoris in 46 cases and a history of congestive heart failure in 18 cases. In 32 patients both a previous infarction and angina was present. Antianginal medication was not discontinued before the study. In 57 examinations patients were taking beta-blocker medication.

The ECG at rest showed no abnormalities in 83 (48%) of the examinations, an old myocardial infarction in 73 (41%), left ventricular hypertrophy in 8 (4.5%), left bundle branch block in 5 (2.8%) and right bundle branch block in 10 (5.6%).

Dobutamine stress echocardiography: The dobutamine stress echocardiography protocol was approved by the hospital ethics committee and was performed as previously described[7]. In short, after giving verbal informed consent, the patients underwent a resting two-dimensional precordial echocardiographic examination. Standard apical and parasternal views were recorded on video tape and a 12 lead ECG was recorded. Dobutamine was then administered intravenously by infusion pump, starting at 10 μg/kg/minute for 3 minutes, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/minute (stage 4), and continued for 6 minutes. In patients not achieving 85% of their age-predicted maximal heart rate who had no symptoms or signs of ischemia, atropine (starting with 0.25 mg increasing to a maximum of 1 mg) was given intravenously at the end of stage 4, while dobutamine was continued. Throughout dobutamine infusion the ECG was continuously monitored, the 12 lead ECG was recorded each minute and the blood pressure was measured by sphygmomanometry every 3 minutes. The two-dimensional echocardiogram was continuously monitored and recorded on video tape during the final minute of each stage. Quad screen display of digitized images for side by side examination of rest and stress images became routine during the later part of the study. Metoprolol was available and used (1 to 5 mg. i.v.) to reverse the effects

of dobutamine or the dobutamine-atropine combination if these did not revert spontaneously and quickly. Atropine was used as an antidote if bradycardia and hypotension occurred. Off-line assessment of echographic images was performed by two experienced investigators without knowledge of the patients' clinical data but with knowledge of the doses of dobutamine and atropine used. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessments, and a majority decision was achieved. For this semi-quantitative assessment the left ventricular wall was divided into 14 segments[19] and each was scored using a 4 point scale: 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic. An increase in score between rest and stress in 1 or more segments, that is a new or worsened wall motion abnormality, constituted a positive test. Absence of a hyperkinetic response to dobutamine was not considered as a positive result.

Interruption criteria for the test were: an obvious new wall motion abnormality, horizontal or downsloping ST depression >2mm at 80 ms after the J-point, ST-elevation, significant chest pain, any symptomatic hypotension a reduction in systolic blood pressure >40 mmHg from that at rest, decrease of heart rate ≥10 beats per minute from that at rest or any side effect regarded as being due to dobutamine. A new wall motion abnormality was considered as an interruption criteria, in the absence of side effects or other markers of ischemia, only if it was severe and extensive.

We have previously shown excellent inter- and intra-observer reproducibility of interpretation of stress echocardiography, of 91 and 92% respectively[20]. In addition, the reproducibility of wall motion abnormalities during dobutamine-atropine stress echocardiography was 100% in 23 patients who underwent two serial studies on different days[21].

Follow up: patient data were collected during the hospital stay and outpatient clinic from hospital records and written information of general physicians. Perioperative cardiac events were those events occurring in the first 30 days after surgery. All cardiac events were investigated by a physician unaware of patient's stress test results. Cardiac events consisted of cardiac death, nonfatal myocardial infarction, unstable angina pectoris. Cardiac death was defined as death due to myocardial infarction, cardiac arrhythmia or congestive heart failure confirmed by clinical data, cardiac isoenzymes, ECG and if possible autopsy. Nonfatal myocardial infarction was defined by clinical data, cardiac isoenzymes and ECG. Unstable angina pectoris was defined by chest pain at rest and transient ECG changes.

Statistical analysis: Univariate analysis for categorial variables was performed using the chi-square test with Yates correction or Fisher's exact test. Continuous variables were analyzed using Student's *t* test. Stepwise logistic regression models were fitted to identify independent predictors of side effects and/or

cardiac events (all variables, clinical data (age, sex, angina, hypertension, congestive heart failure, smoking, diabetes mellitus, history of previous infarction) and stress test results (rest wall motion abnormalities, new wall motion abnormalities, angina and/or electrocardiographic changes during stress), regardless of significance from the univariate analysis were entered into the multivariate analysis). The difference in risk was expressed as the odds ratio (O.R.) with the corresponding 95% confidence intervals (C.I.). Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

To determine the predictive value for late cardiac events of resting wall motion score index we used receiver operator curves (ROC curves). In these curves, sensitivity vs specificity of a test are plotted, where sensitivity is a fraction of positive classification for all patients who satisfy the endpoint criteria and specificity is the fraction of all negative classifications for all patients who satisfy the non-endpoint criteria. These curves provide a direct comparison of their results over the entire range of measurements. The best "cut-off" point was selected with the highest sum of sensitivity and specificity.

Results

The dobutamine-atropine stress test was attempted 179 times. In 2 patients no adequate echo images could be recorded, both patients had severe pulmonary disease. These examinations were excluded from the study, giving a total number of 177 examinations.

In 165 tests (93%) target heart rate was reached. In 12 examinations the test was prematurely stopped because of: 1) severe chest pain 5 (2.7%), 2) ECG changes 1 (0.6%), 3) hypotension 2 (1.1%), 4) cardiac arrhythmias (paroxysmal atrial fibrillation) 2 (1.1%) and chills 2 (1.1%) (table 1). The maximum dobutamine dose used was 10 μg/kg/min in 1 examination, 20 μg/kg/min in 9 examinations, 30 μg/kg/min in 42 examinations and 40 μg/kg/min in 125 examinations. In 47/177 examinations atropine was added to the maximum dose of dobutamine. Atropine was used more often in patients on beta blocker medication (O.R. 4.7, 2.2-10.2) then in patients off beta blockers.

Hemodynamic changes during dobutamine-atropine stress test:
Heart rate, beats per minute: resting heart rate was 73 ± 13 (177 examinations), increasing to 114 ± 25 during peak dobutamine infusion and 125 ± 17 (47 examinations) during combination of dobutamine and atropine.
Systolic blood pressure, mmHg: resting systolic blood pressure was 145 ± 25 (177 examinations), increasing to 149 ± 29 during peak dobutamine infusion and 150 ± 29 (47 examinations) during combination of dobutamine and atropine.

Diastolic blood pressure, mmHg: resting diastolic blood pressure was 81 ± 13 (177 examinations), decreasing to 74 ± 20 during peak dobutamine infusion and 77 ± 15 (47 examinations) during combination of dobutamine and atropine. There were no new side effects (cardiac arrhythmias and hypotension) after atropine addition (O.R. 1.6, 0.4-6.0).

Side effects: Hypotension (decrease of systolic blood pressure >20 mmHg compared to baseline) and cardiac arrhythmias were the most frequently observed side effects of the dobutamine-atropine stress test (table 2).

Table 1 Reason for termination dobutamine-atropine stress test

indication	no.
Target heart rate	165 (93%)
Severe chest pain	5 (2.7%)
Chills	2 (1.1%)
Severe hypotension	2 (1.1%)
Cardiac arrhythmias	2 (1.1%)
ECG changes	1 (0.6%)

Hypotension = systolic blood pressure decrease of >40 mmHg during test compared to base line; cardiac arrhythmias = paroxysmal atrial fibrillation.

Table 2 Side effects during dobutamine-atropine stress test

Arrhythmias		
	paroxysmal atrial fibrillation	4
	premature ventricular complexes	21
	non sustained ventricular tachycardia	3
Hypotension		8
Chills		5
Hypertension		3
Bradycardia		2

Bradycardia = decrease heart rate >10 beats per minute compared to base line during test; hypertension = increase systolic blood pressure of >220 mmHg; hypotension = decrease systolic blood pressure of >20 mmHg compared to base line.

Hypotension, occurred in 8 examinations. In only 2 patients was the test stopped because of symptomatic hypotension together with bradycardia. There was no correlation between the occurrence of hypotension and clinical data or stress test results. The occurrence of hypotension was not related to low or high dose dobutamine or to the addition of atropine (O.R. 1.6, 0.3-7.9).

Cardiac arrhythmias occurred in 28 examinations: three patients experienced non-sustained ventricular tachycardia, twenty-one experienced multiple premature ventricular complexes and four patients developed paroxysmal atrial fibrillation. The test was primarily stopped due to arrhythmias in 2 examinations; both patients experienced paroxysmal atrial fibrillation and were hemodynamicly compromised. Both patients who developed atrial fibrillation responded quickly to metoprolol i.v. and one also was digitalized. There were no deaths or myocardial infarctions.

Dobutamine-induced cardiac arrhythmias were not correlated with stress test results or clinical data. Hypotension occurred more often during arrhythmias (O.R. 6.3, 2.5-16). There was no correlation between atropine addition and arrhythmias (O.R. 1.2, 0.2-6.0).

Chills occurred in 5 patients, causing an interruption of the stress test in 2 (1.1%) patients. Bradycardia occurred in 2 patients accompanied by hypotension, both with stress-induced inferior wall ischemia. Both patients were given atropine (0.25 mg/i.v.) combined with tilting of legs and recovered without complications.

During the stress test new wall motion abnormalities, a sign of myocardial ischemia, occurred in 50 examinations of which 19 occurred after the addition of atropine. In 15 examinations there was a worsening of an already existing wall motion abnormality, while in 35 there were no resting abnormalities.
Chest pain occurred in 33 examinations. ECG changes consisted of ST elevation in 11 and ST depression in 34 examinations.
The stress test was nondiagnostic, no target heart rate or sign or marker of ischemia achieved, in 6 examinations. In 2 patients there were no adequate echo images, in 2 cases chills occurred and in 2 atrial fibrillation without ischemia. The stress test yielded a feasibility of 96.6%.

Follow up: One hundred-sixty-six patients were followed after the stress test for 16 ± 6 (mean ± SD) months. No patient was lost to follow up other then four patients who underwent noncardiac vascular surgery and had a perioperative fatal myocardial infarction. After stress test 34 cardiac events occurred. 12 cardiac events occurred perioperatively (4 cardiac death, 3 myocardial infarction and 5 unstable angina) all in patients with a positive stress test[18]. Twenty-two cardiac events occurred during late follow-up. Fourteen events occurred in the group of patients who were referred for chest pain complaints (4 cardiac death, 4 myocardial infarction and 6 unstable angina). 8 patients experienced late cardiac events after surgery (3 cardiac death, 2 myocardial infarction and 3 unstable angina).

The correlation of perioperative and late cardiac events, clinical data and stress test results by univariate analysis is presented in table 3.

Table 3 Univariate analysis of clinical data and stress test results for prediction for perioperative and late cardiac events in 177 patients

Events	perioperative		late follow-up	
	odds ratio	95% C.I.	odds ratio	95% C.I.
History of angina	4.2	1.0-17	2.6	1.1-6.2
Hypertension	1.6	0.4-6.9	1.1	0.4-2.5
History of previous MI	1.4	0.3-6.1	2.1	0.9-4.8
Diabetes mellitus	0.7	0.1-6.0	0.5	0.1-1.8
Smoking	0.6	0.1-2.6	0.7	0.2-1.7
New wall motion abnormalities	51	6-434	3.4	1.4-8.1
Wall motion abnormalities at rest	4.1	1.1-16	2.3	1.0-5.9
Angina during test	0.9	0.1-3.0	1.8	0.6-4.8
ST changes during test	2.3	0.9-5.8	1.8	0.7-4.3
Atropine addition	2.2	0.5-9.7	1.4	0.6-3.5

Wall motion abnormalities at rest = wall motion score index ≥1.12; C.I. = confidence interval.

New wall motion abnormalities had a sensitivity of predicting perioperative cardiac events of 100% and a specificity of 83%, with a positive predictive value of 43% and a negative predictive value of 100%.
New wall motion abnormalities had a sensitivity of predicting late cardiac events of 64% and a specificity of 77%, with a positive predictive value of 30% and a negative predictive value of 93%.
By multivariate analysis of all clinical data and stress test results, only new wall motion abnormalities were predictive for perioperative and late cardiac events (table 4).

Table 4 Multivariate regression analysis of stress test results and prognostic value for perioperative and late cardiac events in 177 patients.

Events	perioperative		late follow-up	
	odds ratio	95% C.I.	odds ratio	95% C.I.
New wall motion abnormalities	51	5.8-454	5.2	2.0-14

C.I. = confidence interval.

Discussion

Elderly patients comprise an increasing large part of our patient population[1], and often have generalized atherosclerosis. Significant coronary artery disease increases the risk of perioperative cardiac complications in surgical candidates[22], and adversely affects long-term prognosis[23]. However, coronary disease may be difficult to detect in elderly patients, because exercise tolerance is frequently limited by noncardiac disease[22]. Therefore, stress tests which do not require physical exercise are likely to have an additional diagnostic and prognostic value in the elderly.

Pharmacological stress testing is an attractive alternative to exercise testing. Dipyridamole, combined with either myocardial perfusion scintigraphy or echocardiography has been widely used for the evaluation of coronary artery disease[12-15,18,24,25]. The safety of dipyridamole stress-testing is also well established. In a multi-centre study, Picano et al.[26] found that significant complications occurred in only 7/10.451 (0.07%) patients who underwent high-dose dipyridamole echocardiography. Three patients became asystolic, two had a myocardial infarction, one developed ventricular tachycardia and one had pulmonary edema. There was one death (0.01%).

Dobutamine has also been used as a pharmacologic stressor, and dobutamine stress echocardiography has been shown to have both diagnostic and prognostic value in patients with coronary artery disease[14,15]. Dobutamine increases myocardial oxygen demand by its positive inotropic and chronotropic effect[9]. There is usually no effect on the blood pressure as peripheral vasodilatation and vasopressor effect are balanced. These effects are mediated by stimulation of β_1,β_2 and α_1 adrenoreceptors, respectively. The chronotropic and inotropic effects are the most important factors for induction of myocardial ischemia[9,10].

The sensitivity of dobutamine stress testing may be diminished if an adequate heart rate (85% of age-adjusted maximum) is not achieved[7]. This problem may arise in patients who are taking beta blocker medication and in elderly[16]. The

addition of atropine increases the sensitivity of dobutamine stress testing by allowing target heart rate to be achieved in a greater proportion of patients[7]. We have had extensive experience with dobutamine and dobutamine-atropine stress echocardiography[7,12,18,20,21]. The current study extends our previous observations to a population of patients aged ≥70 years. Our results suggest that, dobutamine stress echocardiography is safe and useful for risk stratification in elderly patients with suspected or proven coronary artery disease.

It has been suggested that the chronotropic response to catecholamines is diminished in the elderly[14,17]. This may reflect an attenuated response to ß-adrenergic stimuli, and/or increased vagal tone during stress. This study demonstrates that dobutamine-atropine testing can overcome this theoretical limitation. Ninety-three percent of our patients achieved target heart rate, despite that 32% were also taking ß-adrenergic blocking agents at the time of testing. The use of atropine is particulary important in this regard, as only 73% of patients achieved their target heart rate before it was added.

No sustained or irreversible side effects occurred in this study of 177 septua- and octogenarians. This suggests that dobutamine stress testing is relatively safe in elderly patients, even if "potentiated" with atropine. Hypotension and transient cardiac arrhythmias were the most common adverse events. The test was discontinued because of hypotension in two patients, both of whom also had a bradycardia and electrocardiographic evidence of myocardial ischemia. Both patients responded favourably to intravenous atropine and elevation of their legs. Paroxysmal atrial fibrillation occurred in four patients, leading to premature cessation of the test in two. These episodes responded promptly to intravenous metoprolol. Significant minor side-effects appeared to be more common in this study, than in the large multicentre study of dipyridamole reported by Picano et al.[26]. This may reflect either the different drugs used (dobutamine-atropine vs. dipyridamole), or the different populations studied. A higher incidence of side-effects might be expected in our elderly patients, the majority of whom were studied because of significant vascular disease requiring surgery. A direct comparison of dobutamine and dipyridamole stress testing in elderly patients would be required to determine if there is an important difference in the safety of the two techniques.

In a previous study of 136 consecutive vascular surgery candidates, we found that new wall motion abnormalities induced by dobutamine-atropine stress echocardiography were the best predictor of perioperative cardiac complications[18]. This study extends this observation to a group of 106 vascular surgery patients ≥70 years of age (55 of these were included in the previous publication). Within this group of elderly patients, no clinical feature was predictive of outcome. Multivariate regression analysis indicated that new wall motion abnormalities detected by dobutamine-atropine stress echocardiography were highly predictive of perioperative cardiac events (odds ratio 51, CI 5.8-

454) in the elderly. Other stress test results such as ST-segment change or chest pain during the test were not predictive. As in the previous study, clinical variables were not independent predictors of perioperative cardiac events. Elderly vascular surgery patients who exhibit new wall motion abnormalities on dobutamine-atropine stress echocardiography are at great risk of perioperative cardiac complications. They require careful perioperative management aimed at reducing this risk.

The most important new finding of this study, is that conditional to elderly patients new wall motion abnormalities occurring during dobutamine-atropine stress echocardiography independently predicted not only perioperative events in candidates for vascular surgery but also late cardiac events, in elderly patients referred either for the diagnosis of chest pain or prior to major vascular surgery (odds ratio 5.2, CI 2.0-14) by multivariate regression analysis). Clinical variables and other stress test results were not independently predictive of cardiac death, myocardial infarction or unstable angina pectoris occurring during a follow-up of 16 ± 6 months (range 1-28 months). The positive predictive value of new wall motion abnormalities for late cardiac events was 30% ± 14%, and the negative predictive value was 93% ± 5%. Our data indicate that elderly patients with positive dobutamine-atropine stress echocardiograms may require more careful follow-up, and/or intervention to prevent late cardiac events.

Left ventricular dysfunction is considered to be a powerful predictor of cardiac morbidity, both perioperatively and during follow-up in nonsurgical patients with significant coronary disease[22]. However, left ventricular wall motion score at rest did not independently predict survival in our study. There are two possible explanations for this finding. First, by studying an elderly population, we may have selected patients who were long-term survivors of left ventricular dysfunction. Second, there were relatively few patients with severe left ventricular dysfunction in our study (10 cases with a wall motion score at rest of ≥1.70).

Our experience indicates that dobutamine-atropine stress echocardiography is a safe and useful technique in elderly patients. It provides information regarding the patient's present cardiac condition as well as prognostic information regarding the risk of perioperative and/or late cardiac events. Because it is relatively inexpensive, highly sensitive[11] and potentially more widely available then nuclear cardiology techniques, pharmacological stress echo should be considered as the noninvasive method of choice for evaluation of elderly patients with suspected coronary artery disease who are unable to perform an exercise test.

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CHAPTER 9

DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHY AND CLINICAL DATA FOR PREDICTING LATE CARDIAC EVENTS IN PATIENTS WITH SUSPECTED CORONARY ARTERY DISEASE[1]

(Short title: prognostic information of dobutamine-atropine stress echocardiography)

Don Poldermans*, MD, Paolo M Fioretti, MD, FESC, Eric Boersma, BSE, Jan H. Cornel, MD, Filip Borst*, MD, Erik GJ Vermeulen*, Mariarosaria Arnese, MD, Abdou El-Hendy, MD, Jos RTC Roelandt, MD, FACC.

From the Thoraxcenter and Department of Surgery*, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, the Netherlands.

Abstract

Purpose: To compare the relative value of clinical variables with dobutamine-atropine stress echocardiography to predict cardiac events during long-term follow up. Dobutamine stress echocardiography is increasingly used for detection of coronary artery disease, but little is known of its prognostic value. *Patients and Methods*: 430 patients, 310 men, mean age 59 years (range 22-90) were enroled in the study. Patients were referred for chest pain complaints and were unable to perform an adequate exercise stress test. All patients underwent dobutamine-atropine stress test (incremental dobutamine infusion 10-40 μg/kg/minute, continued with atropine 0.25-1 mg i.v. on top if necessary to achieve 85% of the age predicted maximal heart rate, without symptoms or signs of ischemia) and clinical cardiac evaluation. Follow-up was 17 ± 5 months

[1] Am J Med, accepted for publication

with a minimum of six months; three patients were lost to follow-up. Cardiac events were defined as cardiac death, cardiac death or infarction and coronary revascularisation.
Results: Seventy-nine cardiac events occurred in 76 patients: cardiac death (n = 11), non fatal myocardial infarction (n = 18) and coronary revascularisation (n = 50). By multivariate regression analysis the prognostic value of the stress test additional to common clinical variables was assessed. 1) Cardiac death was predicted by age ≥70 years (odds ratio 5.6, 1.5-20) or new wall motion abnormalities in a study that is normal at rest (odds ratio 4.1, 1.1-15), 2) Death or myocardial infarction was predicted by a history of myocardial infarction (odds ratio 4.8, 1.8-13) or age ≥70 years (odds ratio 2.3, 1.1-5.4), stress test outcome provided no additional information. 3) If all events were combined only stress test results were prognostic: new wall motion abnormalities in a study that is normal at rest (odds ratio 3.1, 1.9-5.1), wall motion abnormalities at rest (wall motion score at rest ≥1.12) (odds ratio 2.5, 1.4-4.0) or any new wall motion abnormalities during stress (odds ratio 2.0, 1.4-3.8). The positive predictive value of any new wall motion abnormality during stress for all late cardiac events was 25% (95% CI 19-31) with a negative predictive value of 87% (95% CI 83-91).
Conclusion: In a large cohort of unselected patients with chest pain syndromes new wall motion abnormalities induced by dobutamine provide additional information for late cardiac events, independent of clinical variables.

Key-words: dobutamine-atropine stress echocardiography- prognostic information- late cardiac events.

Introduction

In patients with suspected coronary artery disease numerous tests provide prognostic information for late cardiac events in addition to clinical data. These include ambulatory ST segment monitoring[1], exercise electrocardiography[2,3], radionuclide ventriculography[4], thallium perfusion scintigraphy[5,6,7] and coronary angiography[8].

Dobutamine-atropine stress combined with echocardiography has been recently proposed for the diagnosis of coronary artery disease by detection of ischemia-induced transient wall motion abnormalities[9-13]. Dobutamine has both positive inotropic and chronotropic effects on the heart by stimulating β_1, β_2 and α_1 adrenoreceptors. The increase of myocardial oxygen demand might induce myocardial ischemia. The test is relative inexpensive, widely available, independent of physical exercise capacity, safe[14] and provides diagnostic information for coronary artery disease[9]. A few recent studies[15-17] suggest that the test also has prognostic value, but only one full paper addresses this issue

in a study on patients referred for chest pain. Prognostic information for late cardiac events may be valuable for risk stratification, and the selection of patients for additional coronary angiography. Clinical variables are often insufficient due to latent coronary artery disease, particularly in patients with limited exercise capacity. Stress electrocardiographic testing provides prognostic information for cardiac events, it may have limitations for detecting residual ischemia in case of resting ECG abnormalities[4].

The aim of our study was to assess the relative prognostic value of clinical variables and dobutamine-atropine stress echocardiography in 430 patients referred for chest pain syndromes during 17 months follow up.

Methods

Patient characteristics: 430 patients (310 men, age range 22 to 90 years, mean 61) with known or suspected coronary artery disease were examined, from 1990 until 1992 at the Thoraxcenter. All patients were referred for chest pain complaints (50% from the outpatient clinic), no patient had a recent infarction (<3 months). Clinical data examined were: age, sex, previous infarction, angina pectoris, hypertension, smoking, cardiac arrhythmias, history of congestive heart failure and medication use. A history of previous myocardial infarction was present in 207 patients, typical angina pectoris in 238 patients. Both angina and previous infarction was present in 97 patients. Antianginal medication was continued during the study. In 212 examinations patients were using beta blockers.

The ECG at rest showed no abnormalities in 209 (49%) of the cases, a previous myocardial infarction in 192 (45%), left ventricular hypertrophy in 10 (2.3%), left bundle branch block in 12 (2.7%) and right bundle branch block in 7 (1.6%).

Dobutamine stress echocardiography:The dobutamine-atropine stress echocardiography protocol was approved by the Hospital Ethics Committee and was performed as previously described[13]. In short, after giving verbal informed consent, the patients underwent a resting two-dimensional precordial echocardiographic examination. Standard apical and parasternal views were recorded on video tape and a 12 lead ECG was recorded. Dobutamine was then administered intravenously by infusion pump, starting at 10 μg/kg/minute for 3 minutes, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/minute (stage 4), and continued for 6 minutes. In patients not achieving 85% of their age-predicted maximal heart rate who had no symptoms or signs of ischemia, atropine (starting with 0.25 mg increasing to a maximum of 1 mg) was given intravenously at the end of stage 4, while dobutamine was continued. Throughout dobutamine infusion the ECG was continuously monitored, the 12-

lead ECG was recorded each minute and the blood pressure was measured by sphygmomanometry every 3 minutes. The two-dimensional echocardiogram was continuously monitored and recorded on video tape during the final minute of each stage. Quad screen display for side by side examination of rest and stress images have become routine during the last 200 studies. Metoprolol was available and used (1 to 5 mg. i.v.) to reverse the effects of dobutamine or dobutamine-atropine combination if these did not revert spontaneously and quickly. Atropine was used if bradycardia and hypotension occurred. Off-line assessment of echographic images was performed by two experienced investigators without knowledge of the patients' clinical data but with knowledge of the doses of dobutamine and atropine used. When there was disagreement between the two investigators, a third one viewed the images without knowledge of the previous assessments, and a majority decision was achieved. For this semi-quantitative assessment the left ventricular wall was divided into 14 segments (figure 1) and each was scored using a 4 point scale: 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic[18]. An increase in score between rest and stress in 1 or more segments constituted a positive test. All new wall motion abnormalities during stress, group I, were divided into 3 sub groups: II = a new wall motion abnormality in a study that is normal at rest, III = rest wall motion abnormality with remote ischemic response to stress, IV = worsening of preexisting wall motion abnormality during stress.

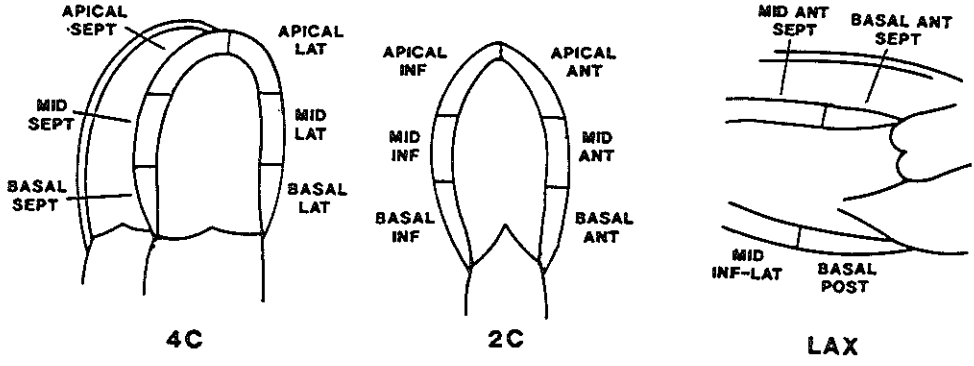


Figure 1 The 14-segment model of the left ventricle. Lax = parasternal long axis, 4C = apical four chamber view, 2C = apical two chamber view, inf = inferior, sept = septum and lat = lateral

Interruption criteria for the test were: horizontal or downsloping ST depression >2mm at 80 ms after the J point, ST elevation, serious cardiac arrhythmias, significant chest pain, reduction in systolic blood pressure >40 mmHg from that at rest, a systolic blood pressure <90 mmHg, hypertension (systolic blood pressure ≥220 mmHg), or any side effect regarded as being due to dobutamine.

A new wall motion abnormality was considered as an interruption criteria only if it was severe and extensive. As our experience grew we were more aggressive in continuing the stress test until target heart rate was reached independent of mild new wall motion abnormalities. We have previously shown excellent inter and intra-observer reproducibility of interpretation of stress echocardiography, of 91 and 92% respectively[19]. In addition, the reproducibility of wall motion abnormalities during dobutamine-atropine stress echocardiography was 100% in 23 patients who underwent two serial studies on different days[20].

Follow-up: follow-up data were obtained over 17 ± 5 months with a minimum of 6 months. During follow up events defined as cardiac death, nonfatal myocardial infarction and coronary revascularisation (bypass surgery or transluminal angioplasty) were collected. All cardiac events were assessed by physicians unaware of patients former stress test results, by investigation of hospital records and correspondence with their general physician.

Statistical analysis: Univariate analysis for categorial variables (clinical data, (age, sex, previous infarction, angina pectoris, hypertension, cardiac arrhythmias and anti anginal medication) and stress test results, (angina, ST segment changes, new wall motion abnormalities during stress and rest wall motion abnormalities) was performed using the chi-square test with Yates correction or Fisher's exact test. Continuous variables were analyzed using Student's t test, when appropriate. Kaplan-Meier curves were plotted to summarize follow-up data. To compare and visualize the predictive value of rest wall motion abnormalities, we used receiver operator characteristics curves (ROC curves) to find the best cut-off point. In these curves, sensitivity vs specificity of a test are plotted, where sensitivity is a fraction of positive classification for all patients who satisfy the endpoint criteria and specificity is the fraction of all negative classifications for all patients who satisfy the non-endpoint criteria. These curves provide a direct comparison of their results over the entire range of measurements. Stepwise logistic regression models were fitted to identify independent clinical predictors of late cardiac events and the additional prognostic value of stress test results. In case of more then one events in the same patient, the worst cardiac event was considered for the analysis of the results.The difference in risk was expressed as the odds ratio (OR) with the corresponding 95% confidence intervals (CI). Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

Results

Four hundred thirty two patients were enroled in the study. In 2 patients no adequate echo images could be recorded, both patients had severe pulmonary disease and were excluded from the study.

In 430 patients clinical data and stress test results were obtained. In 384 tests (89%) target heart rate was reached. In 46 (11%) examinations the test was prematurely stopped because of: 1) severe chest pain 23 (5%), 2) ECG changes 10 (2%), 3) echographic recorded new wall motion abnormalities 2 (0.4%), 4) severe hypotension (systolic blood pressure decrease >40 mmHg compared to base line) 2 (0.4%), 5) cardiac arrhythmias (1 ventricular fibrillation, 1 sustained ventricular tachycardia and 4 paroxysmal atrial fibrillation) 6 (1.2%) and chills 3 (0.6%). All side effects though not always causing interruption of the test or occurring during recovery are shown in table 1. Dobutamine dose used during test was 20 μg/kg/minute in 7 patients, 30 μg in 42 patients and 40 μg in 381 patients.

Table 1 Side effects during dobutamine-atropine stress test in 430 patients

arrhythmias		
	paroxysmal atrial fibrillation	5 (1%)
	non sustained ventricular tachycardia	5 (1%)
	ventricular fibrillation	1 (0.2%)
	sustained ventricular tachycardia	1 (0.2%)
chills		11 (2.5%)
hypotension ≥20- <40 mmHg		10 (2.3%)
hypotension ≥40 mmHg		2 (0.4%)

hypotension = decrease systolic blood pressure compared to baseline.

In 176/430 examinations atropine was added in addition to the maximum dose of dobutamine. Atropine addition was more often used in patients on beta blocker medication (O.R. 4.9, 95% C.I. 3.1-7.7 patients on vs off beta blockers). Chest pain during stress occurred in 131 (30%) patients and ST segment changes in 154 (36%).

Any new wall motion abnormalities occurred in 182 (43%) patients (group I). Three subgroups were analyzed. In 149 patients there was a normal rest echocardiogram and ischemic response to stress (group II), in 31 patients there were rest wall motion abnormalities with remote ischemic response to stress (group III) and in 39 patients there was a worsening of preexisting wall motion abnormalities (group IV).

Side effects:
Besides chest pain, hypotension and cardiac arrhythmias were the most important side effects of dobutamine-atropine stress test (table I). There was no correlation between side effects and the addition of atropine (odds ratio 0.7, 0.2-1.9)

When hypotension was defined as a decrease of systolic blood pressure of >20 mmHg compared to base line this occurred in 12 examinations. Though most patients were able to continue the test without discomfort, in 2 patients the test was stopped because of severe and symptomatic hypotension (decrease of systolic blood pressure >40 mmHg).

The occurrence of hypotension was not related to the dose of dobutamine, atropine addition or induction of ischemia.

Significant and/or symptomatic cardiac arrhythmias occurred in 12 examinations: one patient developed ventricular fibrillation, one patient sustained ventricular tachycardia, 5 patients experienced non-sustained ventricular tachycardia and 5 patients had paroxysmal atrial fibrillation. The test was primarily stopped due to arrhythmias in 6 examinations. There were no deaths or myocardial infarctions. All patients who developed atrial fibrillation responded quickly to metoprolol i.v. and one patient was digitalized as well.
Follow-up: three patients were lost to follow-up. Seventy-nine cardiac events occurred during follow-up in 76 patients. Eleven patients experienced cardiac death and 18 a nonfatal infarction. In 50 a coronary revascularisation was performed (bypass surgery or a transluminal angioplasty). Seven patients had a stroke and there were 6 noncardiac deaths.

The univariate analysis of clinical data and stress test results to predict cardiac death, cardiac death or myocardial infarction, and all cardiac events is presented in table II. Cardiac death correlated with 1) age ≥70 years (odds ratio 5.1, 1.5-17), new wall motion abnormalities group II (odds ratio 3.5, 1.1-12), all other variables were not predictive.

Cardiac death or myocardial infarction was related to a 1) history of myocardial infarction (odds ratio 5.8, 1.9-20), 2) age ≥70 years (odds ratio 2.3, 1.1-5.1), 3) new wall motion abnormalities group III (odds ratio 4.0, 1.5-11), 4) rest wall motion abnormalities (wall motion score index at rest ≥1.12 was determined by ROC curves as best cut-off point) (odds ratio 2.9, 1.3-6.6) or 5) new wall motion abnormalities group II (odds ratio 2.2, 1.1-4.7).
When cardiac events were combined they were significantly correlated with 1) new wall motion abnormalities group II (odds ratio 3.0, 1.8-5.0), 2) rest wall motion abnormalities (wall motion score index at rest ≥1.12)(odds ratio 2.7, 1.6-4.5), 3) New wall motion abnormalities group I and III (odds ratio 2.3, 1.4-3.8 resp. 2.3, 1.5-11) (table III). The positive predictive value of any new wall motion response to stress for all late cardiac events was 25% (95% C.I. 19-31) and a negative predictive value 87% (95% C.I. 83-91).

Multivariate regression analysis was performed on all clinical variables and stress test results. Stress test results were analyzed for their additional prognostic value on top of common clinical variables. There was a significant correlation between 1) cardiac death and age ≥70 years (odds ratio 5.6, 1.5-20) or new wall motion abnormalities group II (odds ratio 1.1-15) 2) cardiac death or myocardial infarction and a history of a previous myocardial infarction (odds ratio 4.8, 1.8-13) or age ≥70 years (odds ratio 2.3, 1.1-5.4) and 3) all cardiac events and new wall motion abnormalities group II (odds ratio 3.1, 1.9-5.1), rest wall motion abnormalities (wall motion score index at rest ≥1.12) (odds ratio 2.5, 1.4-4.0) or new wall motion abnormalities group I (odds ratio 2.0, 1.4-3.8) (table III).

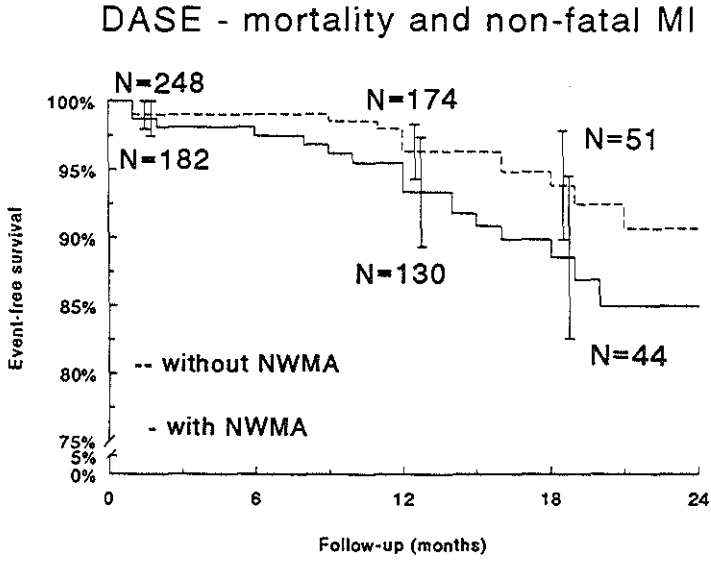
When patients with and without myocardial infarction were compared (table IV), there were more cardiac death and myocardial infarctions in the group with a previous myocardial infarction ($p < 0.001$). In 147 patients without a previous myocardial infarction and a negative dobutamine-atropine stress test no cardiac death or myocardial infarction occurred during follow up of 17 months. Event-free survival curves for patients with and without new wall motion abnormalities are presented in figure 2, (end-points were cardiac death and myocardial infarction) and figure 3 (all cardiac events). For all cardiac events there is a significant difference in event-free survival in patients with new wall motion abnormalities.

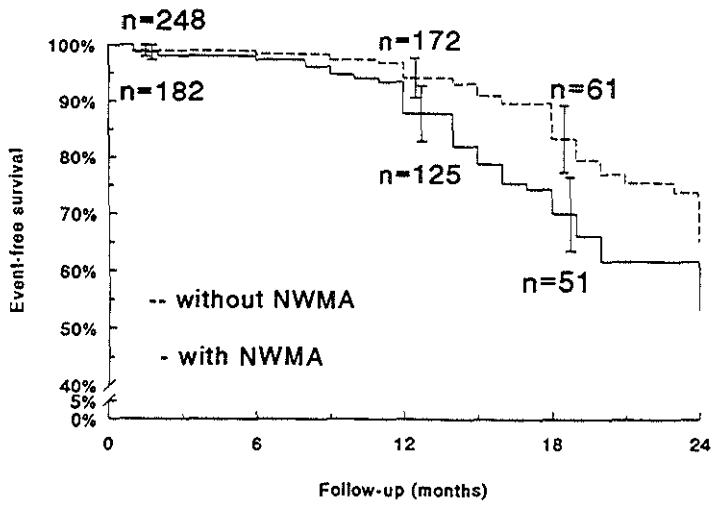
Discussion

Noninvasive risk stratification in patients with suspected or proven coronary artery disease is of increasing relevance, from one side to the rapid increase of the "therapeutic" modalities and on the other side to the economical constraints we are faced to. Pharmacological stress echocardiography is a very promising tool in this context, since it is widely available and can be applied in almost all patients and is less expensive then other imaging methods, like perfusion scintigraphy[22].

In this study we tested the hypothesis that dobutamine-atropine stress echocardiography provides superior information to clinical variables alone, to predict the late clinical outcome in a cohort of 430 patients referred for chest pain at one centre.

As far as we are aware of, this is the largest study group so far with dobutamine-atropine stress echocardiography reported for this purpose. Further since, in our study dobutamine-atropine stress test was considered as a research tool, and the test outcome was not used for clinical management by the attending physicians, thus a referral bias for coronary arteriography and subsequent revascularisation has been avoided.





Figures 2 and 3 Kaplan-Meier curves for cardiac death and myocardial infarction (figure 2) and all events (figure 3) during follow-up by results of dobutamine-atropine stress test (with or without new wall motion abnormalities). Each plot represents the cumulative percentage of patients remaining events free. Vertical lines representing 95% confidence interval. For all cardiac events there is a significant difference in event-free survival in patients with new wall motion abnormalities.

Our data show that new wall motion abnormalities during dobutamine-atropine stress echocardiography provide an additional prognostic information on top of clinical variables, when cardiac death and all cardiac events were considered. As expected, elderly age (≥70 years) was the strongest predictor of cardiac death, while new wall motion abnormalities during stress with a normal rest echo provided additional prognostic information. When non fatal infarction was added to death as an end-point the predictive power of echo parameters were lost. This is consistent with the lack of predictive value for non fatal infarction of any stress test[21] and can be explained by a sudden progression, like a plaque rupture of a moderate lesion that is often undetected by the stress test. Common clinical variables as a previous infarction and elderly age were predictive for cardiac death or non fatal infarction.

If all cardiac events were combined only stress test results provided independent information for late events. Stress echo results were most predictive of subsequent events in patients with normal wall motion at rest and an ischemic response to stress (group II). In contrast, the results were not predictive (group III) or less predictive (group IV) in presence of abnormal wall motion at rest. This is not surprising, considering that the interpretation of stress echo is most difficult in patients with abnormal wall motions at rest. This is particularly true in patients with akinetic segments becoming dyskinetic during stress. We have recently demonstrated, using perfusion scintigraphy as a reference method, that this pattern is not consistent with ischemia[23].

Most importantly, echocardiographic results provided additional information beyond clinical data alone. In patients referred for chest pain complaints without a previous myocardial infarction a negative stress test carries a low risk for cardiac death or myocardial infarction.

One study presented as a full paper and two abstracts have addressed to the prognostic value of dobutamine stress echo. Unfortunately the study of Mazeika et al.[15] is difficult to compare with our study. The population studied consisted of younger patients, (54 ± 9 vs 61 ± 8) years, mostly with typical angina, (78% vs 55%) and of limited number (51 vs 430). During follow-up only one patient had a myocardial infarction and there were no cardiac death. Thus their end points consisted mainly of recurrent angina and they found a positive predictive value 78%, 95% CI 62-94. This is higher than what we found for all cardiac events 25%, 95% CI 19-31, but this can be due the very different study group. Also these authors did not specify at what extent the results of the test was used for subsequent therapeutic interventions which were considered as end points. It is important to underscore again that in our study the attending physicians were blinded to the results of the test. The negative predictive value was comparable, 78%, 95% CI 62-94 of the study by Mazeika[15] vs 87%, 95% CI 83-91 in our study.

Two other studies are published in abstract form. The study of Marcovitz et al.[16] consists of 291 patients with a comparable follow up of 15 ± 4 months and

18 cardiac death and 16 myocardial infarctions. Patients with rest wall motion abnormalities 176 vs 291 have a higher incidence of cardiac death 16 vs 2 compared to patients without resting wall motion abnormalities. In patients with a negative test and no rest wall motion abnormalities, (76/291) no cardiac death and only 1 myocardial infarction occurred. This is in perfect agreement with our findings. The study of Kamran et al.[17] consists of 207 patients with a shorter follow up, 9 ± 5.7 months. This study showed by multivariate regression analysis the predictive value of new wall motion abnormalities during stress for cardiac death, although these patients were also assessed for perioperative risk which might create a bias.

Dipyridamole echocardiography has also been used for prognostic stratification. The study of Picano et al.[24] shows similar results to ours, positive predictive value of 36%, 95% CI 30-42 and a negative predictive value of 94%, 95% CI 91-97 for late cardiac events. Dipyridamole thallium scintigraphy has also been used for prognostic evaluation in patients referred for complaints of chest pain[7]. The predictive value for cardiac death or nonfatal infarction is comparable only if new wall motion abnormalities group II, normal rest, ischemic response to stress is considered. Positive predictive value in our study is 10%, 95% CI 5-15 vs 14%, 95% CI 10-18 in the study of Hendel. Both studies show a high negative predictive value, 95%, 95% CI 92-98 vs 96%, 95% CI 93-99. However no head to head comparison between dipyridamole and dobutamine has been done for risk stratification. Therefore, it is unclear which stress modality should be preferred.

Conclusions: In summary, in the present study we found that dobutamine-atropine stress echocardiography applied in patients referred for chest pain complaints, identifies a large proportion of patients with an excellent prognosis if the test is normal. In case of stress induced new wall motion abnormalities, the risk for late cardiac events, and especially cardiac death or coronary revascularisation, is increased.

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Table 2 Association by univariate analysis of clinical data and stress test results with late cardiac events (N = 430)

	Cardiac death	Cardiac death/infarction	All cardiac events
Age ≥70 years	5.1 (1.5-17)	2.3 (1.1-5.1)	1.6 (0.9-2.8)NS
History of infarction	1.6 (0.5-5.5)NS	4.7 (1.7-13)	1.8 (0.9-2.4)NS
History of angina	0.6 (0.2-2.2)NS	0.6 (0.3-1.3)NS	1.4 (0.7-1.9)NS
Diabetes mellitus	0.5 (0.1-1.5)NS	0.5 (0.1-3.5)NS	0.3 (0.1-1.3)NS
Anti-anginal medication	0.5 (0.1-1.8)NS	0.7 (0.4-1.6)NS	1.2 (0.7-2.0)NS
RWMA	1.5 (0.5-5.0)NS	2.9 (1.3-6.6)	2.7 (1.6-4.5)
Angina during stress	1.1 (0.3-3.9)NS	1.9 (0.9-4.0)NS	1.5 (0.9-2.5)NS
NWMA I	2.4 (0.7-8.4)NS	1.7 (0.8-3.6)NS	2.3 (1.4-3.8)
NWMA II	3.5 (1.1-12)	2.2 (1.1-4.7)	3.0 (1.8-5.0)
NWMA III	1.3 (0.2-11)NS	4.0 (1.5-11)	2.3 (1.1-5.2)
NWMA IV	0.5 (0.2-3.1)NS	0.6 (0.4-5.0) NS	2.1 (0.6-6.9)NS

OR = odds ratio; CI = 95% confidence interval; Anti-anginal medication = beta-blockers and/or nitrates and/or calcium antagonists; RWMA = rest wall motion score index at rest ≥1.12; NWMA I = all new wall motion abnormalities; NWMA II = normal rest echo, ischemic response to stress; NWMA III = wall motion abnormalities at rest, remote ischemic response to stress; NWMA IV: worsening preexisting wall motion abnormalities to stress; NS = not significant.

Table 3 Association by multivariate regression analysis of clinical data and stress test results with late cardiac events (N = 430)

	Age ≥70 yrs OR (CI)	MI OR(CI)	RWMA OR (CI)	NWMA I OR (CI)	NWMA II OR (CI)	NWMA III OR (CI)	NWMA IV OR (CI)
Cardiac death	5.6 (1.5-20)	NS	NS	NS	4.1 (1.1-15)	NS	NS
Cardiac death or myocardial infarction	2.3 (1.1-5.4)	4.8 (1.8-13)	NS	NS	NS	NS	NS
All events	NS	NS	2.5 (1.4-4.0)	NS	3.1 (1.9-5.0)	NS	2.3 (1.4-3.9)

OR = odds ratio; CI = 95% confidence interval; MI = history of previous myocardial infarction; RWMA = rest wall motion score index ≥1.12; NWMA I = all new wall motion abnormalities; NWMA II = normal rest echo, ischemic response to stress; NWMA III = wall motion abnormalities at rest, remote ischemic response to stress; NWMA IV: worsening preexisting wall motion abnormalities to stress; NS = not significant.

Table 4 Events according to the presence or absence of a previous myocardial infarction and of the results of dobutamine-atropine stress echocardiography

		death	myocardial infarction	coronary revascularisation	no events	total events
no previous MI N = 223	DSE - N = 147	0	0	10 (7%)	137 (93%)	10 (7%)
	DSE + N = 76	3 (3.9%)	1 (1.3%)	13 (17%)	59 (76%)	17 (24%)
previous MI N = 207	DSE - N = 100	4 (4%)	8 (8%)	9 (9%)	79 (78%)	21 (22%)
	DSE + N = 107	4 (3.7%)	9 (8%)	18 (17%)	76 (70%)	31 (30%)

MI = myocardial infarction; DSE = dobutamine-atropine stress echocardiography.

CHAPTER 10

SUMMARY AND CONCLUSIONS

The dobutamine-atropine stress test has developed from an investigational tool to a practical tool for clinical use. Dobutamine-atropine stress echocardiography is highly sensitive for detection of coronary artery disease and left ventricular dysfunction. In contrast to coronary angiography which detects anatomical abnormalities, stress echocardiography detects functional coronary artery lesions.

The test has been proved to be safe, even in elderly patients. In patients taking beta blocker medication in the majority of patients there is no need of discontinuing this medication. If patients do not reach the test end-point on dobutamine alone and have no signs or markers of ischemia, atropine can be added on top of dobutamine which increases the test feasibility without extra side effects.

Side effects of the stress test consist mostly of hypotension and cardiac arrhythmias. Hypotension is usually mild: a decrease of systolic blood pressure between 20 to 40 mmHg compared to baseline pressure, and most patients are able to complete the test without any discomfort. Hypotension occurs less frequently in patients (1 case) taking beta blockers. Serious cardiac arrhythmias, ventricular fibrillation, sustained ventricular tachycardia and paroxysmal atrial fibrillation occur mostly in patients with a history of ventricular arrhythmias or poor left ventricular function. In these cases caution is warranted and a comparative study with other stress modalities as dipyridamole is needed.

In elderly patients, a group that might benefit most from this new test as it simulates exercise stress, the dobutamine-atropine stress test provides diagnostic information about silent coronary artery diseases and prognostic information for late cardiac events. It is common belief that heart rate responsiveness to ß-adrenoceptor agonists is reduced in elderly people. This is based on studies with isoproterenol induced tachycardia which showed a shift of the dose-response curve in senescent animals and humans. Besides a direct stimulant effect on $ß_1$-adrenoceptors leading to a positive inotropic and chronotropic effect, isoproterenol also has a stimulant effect on peripheral $ß_2$-adrenoceptors leading to vasodilatation. Increased heart rate reflects a combination of direct ß-adrenoceptor stimulation by isoproterenol and vagal activity withdrawal due to peripheral vasodilatation. The higher dose response curves in elderly patients might be partly due to a diminished baroreflex activity. Our study using dobutamine with only minor effect on blood pressure showed a normal heart rate response in elderly patients. In subgroups of patients without a history of coronary artery disease and echocardiographic abnormalities at rest and/or during stress, an increased chronotropic responsiveness to dobutamine was found related to blood pressure changes.

The clinical applications for dobutamine-atropine stress echocardiography are promising. In patients scheduled for elective major vascular surgery the test discriminates patients with a high and very low perioperative cardiac risk. The test also provides prognostic information for late cardiac events after surgery. The predictive value for late cardiac events is less accurate compared to perioperative events which may be related to the different pathophysiology of these late events. In patients referred for chest pain the test can identify myocardial ischemia independent of the patients exercise capacity. A negative test in these patients carries a good prognosis.

Future applications for dobutamine-atropine stress echocardiography are: 1) evaluation of clinical condition and long-term cardiac prognosis especially in elderly patients referred for complaints of chest pain; 2) assessment of cardiac condition in handicapped patients scheduled for rehabilitation; 3) preoperative cardiac risk stratification and 4) evaluation of myocardial viability.

The prognostic value of dobutamine-atropine stress echocardiography is limited to cardiac death and unstable angina pectoris necessitating coronary revascularisation procedures. Myocardial infarction is difficult to predict which is not surprising since stress testing detects flow-limiting coronary artery stenoses but can not identify patients who will develop a thrombus or plaque rupture on top of this lesion.

In disabled patients stress testing will be a useful tool to estimate the cardiac reserve in order to design an appropriate rehabilitation program. Care must be taken in patients with spinal lesions who have a disturbed autonomic nerve system. These patients may have an exaggerated response to dobutamine potentially leading to deep hypotension. In these patients a comparison is

needed with alternative stress modalities like dipyridamole in combination with echocardiography or nuclear scanning.

Patients referred for major vascular surgery are at high risk of perioperative and late cardiac complications. In order to reduce the perioperative risk, patients at high risk must be selected before surgery. Usually only a medical history is taken and a physical examination is performed combined with a electrocardiography. This work-up is inadequate for the selection of high and low risk patients as most patients are unable to perform adequate physical exercise which may conceal coronary artery disease. Also, silent myocardial ischemia is often present especially in diabetic patients who are prone to vascular disease. Numerous investigational tools have been developed and used to select high risk patients before operation, like ambulatory electrocardiographic monitoring, angiocardiography, radionuclide ventriculography and dipyridamole thallium scintigraphy. The perioperative morbidity has been gradually reduced, also in hospitals with a limited preoperative work-up, raising doubts about cost-effectiveness of extensive and expensive cardiac screenings programmes. At present the perioperative cardiac morbidity rate in patients undergoing major vascular surgery is 1-15%, with a mortality rate of 1-5%.

Dobutamine stress echocardiography may have a potential place in preoperative risk stratification in 3 circumstances: 1) patients with a positive test will undergo a coronary revascularisation procedures before major surgery; 2) patients with a positive test are selected for an alternative treatment of their peripheral vascular disease; 3) perioperative management is changed.

Prophylactic coronary artery revascularisation (either coronary artery bypass surgery or PTCA) seems attractive as patients with a successful revascularisation procedure before vascular surgery have nearly the same perioperative risk as "healthy" patients. This would also protect patients in the period after surgery where there is a high incidence of cardiac events. This option has potential draw-backs: 1) patients with a high perioperative risk for vascular surgery will also have a higher risk for coronary revascularisation, although angioplasty may be an alternative to surgery in selected cases with localized coronary lesions; 2) all stress tests currently in use have a low positive predictive value, which would cause a considerable financial and logistic burden to prevent a relatively small number of events and 3) improvement in long-term survival after myocardial revascularisation has been based on studies with a different patient population: low percentage of female patients, young of age and small number of patients with vascular disease which may cast doubt on the overall survival benefit.

An alternative treatment in patients with a positive test is an other option. In selected patients an angioplasty with or without stenting can be performed in stead of major vascular surgery.

A different perioperative management is probably the best option but the question is of course whether any perioperative management programme is available that will indeed decrease perioperative mortality. Considering the decreasing perioperative cardiac morbidity in vascular surgery due to advances in surgical and anaesthetic techniques and considering the morbidity on a waiting list for and also during coronary revascularisation procedures, medical treatment seems an attractive option. Beta blockers are probably first choice, given the pathophysiology of perioperative myocardial ischemia. Only 13% of patients with vascular disease in our group, equally distributed between patients with a positive and negative stress test, are on beta blockers. During operation the use of a short acting beta blocker, like esmolol (t 1/2 = 9 minutes) is attractive. There are now studies being published considering the safety and effectiveness of esmolol during surgery. After operation beta blockers must be continued, as patients usually will have an increased exercise capacity as a result of the operation which may "unmask" coronary artery disease. An alternative option in patients who have contraindications for beta blockers is the use of calcium antagonists.

To test this hypothesis the next step in our research concerning clinical application of dobutamine-atropine stress echocardiography will be to conduct a clinical trial, in which patients selected for elective vascular surgery with a positive stress test will be stratified for conventional perioperative treatment (usually nitroglycerine) versus conventional treatment plus beta blocker medication. In this study not only perioperative events but also late cardiac events should be monitored, for instance over a three year period, in order to assess the feasibility of decreasing perioperative and late morbidity and mortality by intentional use of beta blocker medication peri- and postoperatively.

SAMENVATTING EN CONCLUSIES

Dobutamine-atropine stress echocardiografie heeft zich een plaats verworven in de dagelijkse klinische praktijk. De test combineert informatie over afwijkingen van de linker ventrikel functie in rust en tijdens dobutamine stress. Dobutamine infusie veroorzaakt een toegenomen zuurstofbehoefte van het hart, door een positief inotroop- en chronotroop-effect, waardoor de vraag aan zuurstof het aanbod kan overtreffen en ischemie optreedt. De normale reactie van het hart tijdens inspanning is een systolische verdikking en versterkte binnenwaarts gerichte beweging van het endocard. Myocard ischemie uit zich in regionale gestoorde wandbewegingen zoals hypokinesie, akinesie en dyskinesie. De gevonden afwijkingen tijdens stress geven functionele informatie in tegenstelling tot de anatomische informatie die verkregen wordt door middel van coronair angiografie.

Deze methode van onderzoek is veilig en goed uitvoerbaar, zelfs in oudere patiënten. In patiënten die beta blokkers gebruiken is het niet nodig deze te stoppen voor het onderzoek. Beta blokkers antagoneren gedeeltelijk de werking van dobutamine, echter door de toevoeging van atropine bij die patiënten die geen volledige test behalen, is het vaak toch mogelijk een volledig onderzoek te doen zonder extra bijwerkingen.

Hypotensie en cardiale ritmestoornissen zijn de meest voorkomende bijwerkingen van de test. De hypotensie, meestal mild van aard (vermindering van systolische bloeddruk van 20-40 mmHg ten opzichte van de uitgangswaarde), wordt door de meeste patiënten goed verdragen. Ernstige cardiale ritmestoornissen, ventrikelfibrillatie (1 patiënt), persisterende ventrikel tachycardie en paroxysmaal atriumfibrilleren treden vooral op bij patiënten met een voorgeschiedenis van ventriculaire ritmestoornissen of een slechte linker ventrikel functie. In deze groep is vergelijking met andere pharmacologische "stress" medicatie zoals dipyridamole gewenst.

Vooral de oudere patiënt kan baat hebben van deze nieuwe stress test daar het inspanning nabootst en tevens prognostische waarde heeft. In de literatuur wordt vermeld dat de chronotrope reactie op ß-adrenerge stimulatie verminderd is bij ouderen, dit is in tegenstelling tot de "normale" hart frequentie respons die in dit onderzoek werd gevonden tijdens dobutamine infusie. Deze waarnemingen van een verminderde ß-adrenerge receptor gevoeligheid in de ouderen berusten op onderzoek bij proefdieren en mensen met isoprenaline. Isoprenaline heeft naast een direct inotroop- en chronotroop-effect ook een vaatverwijdend effect zodat de toename in hart frequentie berust op een combinatie van directe stimulatie en indirecte activering van de adrenerge receptor via een baroreflex mechanisme. De verschuiving van de dosis-respons curve bij ouderen kan voor een gedeelte verklaard worden op basis van een verminderde baroreflex functie.

De toepassing van dobutamine-atropine stress echocardiografie is van grote waarde bij patiënten die een uitgebreide vaatoperatie moeten ondergaan. De test heeft een hoge voorspellende waarde voor perioperatieve cardiale complicaties. De prognostische waarde voor cardiale complicaties na de operatie is minder; dit valt te verklaren op basis van een andere pathofysiologie van late cardiale complicaties. De stress test detecteert coronair sclerose, echter wanNeer een totale occlusie zal plaatsvinden is niet te voorspellen.

Toekomstige indicaties voor dobutamine-atropine stress echocardiografie zijn: 1) onderzoek van patiënten verwezen wegens borstklachten, waarbij klachten geobjectiveerd kunnen worden en prognostische informatie wordt verkregen, 2) beoordeling van de cardiale conditie van geïnvalideerde patiënten die een revalidatieprogramma moeten ondergaan, 3) preoperatieve cardiale risico stratificatie, 4) beoordeling van myocard-vitaliteit.

In patiënten verwezen wegens borstklachten geeft de test aan of er ischemie optreedt tijdens stress en tevens prognostische informatie. De aanwezigheid van voorbijgaande wandbewegingsstoornissen tijdens dobutamine is gerelateerd aan cardiale dood en coronaire revascularisatie wegens angina pectoris. Voorspelling van een myocard infarct is op basis van de stress test niet mogelijk, deze is wel gecorreleerd aan een oud infarct en oudere leeftijd (ouder dan 70 jaar). Dit is niet verwonderlijk daar de test coronair afwijkingen kan detecteren, maar niet wanneer deze worden afgesloten door een trombus of plaque ruptuur.

De cardiale conditie van invalide patiënten kan bepalend zijn voor het succes van het revalidatieprogramma. Deze test kan een goede inschatting maken van de cardiale reserve van de patiënt. Voorzichtigheid is geboden bij patiënten met ruggemergletsel waarbij het autonome zenuwstelsel aangedaan kan zijn en gedurende dobutamine infusie versterkte hemodynamische reacties, met name hypotensie, kan optreden.

Patiënten verwezen voor een vaatoperatie hebben een verhoogd peri- en post-operatief cardiaal risico. Dit kan verminderd worden door voor de operatie patiënten met een verhoogd risico te selecteren. Meestal vindt voor de operatie een beperkt cardiaal onderzoek plaats zoals anamnese, lichamelijk onderzoek en ECG. Dit is onvoldoende daar de meeste patiënten slechts een beperkte lichamelijke inspanning kunnen leveren waardoor coronair afwijkingen verborgen blijven. Tevens kan er sprake zijn van "stille" ischemie, vooral bij diabetes mellitus, en juist deze groep heeft frequent vaatziekten. Verschillende methoden worden nu gebruikt om ischemie te detecteren zoals 24-uurs Holter-ST segment monitoring, linker ventrikel ejectie fractie bepaling en dipyridamole-thallium perfussie scintigrafie, waarvan de laatste de meest gebruikte is. Een nieuwe onderzoeksmethode moet naast de bestaande methoden ook rekening houden met een verminderde perioperatieve sterfte tijdens vaatoperaties door een verbeterde chirurgische en anesthesiologische techniek. Deze verandering treedt ook op in klinieken waar een zeer beperkte risico-analyse plaatsvindt. De perioperatieve morbiditeit bij electieve vaatoperaties is 1-15%, de mortaliteit 1-5%.

Dobutamine stress echocardiografie kan een belangrijke plaats innemen bij preoperatieve cardiale risico stratificatie. Ten opzichte van nucleair onderzoek is het voordeliger: er is geen stralenbelasting en het geeft directe informatie tijdens de stress test over de cardiale conditie. Een positieve stress test, voorbijgaande wandbewegingsafwijkingen tijdens dobutamine stress, kan drie mogelijke gevolgen hebben: 1) patiënten met een positieve test ondergaan eerst een coronaire revascularisatie voor de vaatoperatie; 2) patiënten met een positieve test krijgen een alternatieve behandeling en 3) de perioperatieve zorg wordt aangepast bij patiënten met een positieve test.

Coronaire revascularisatie lijkt de meest aantrekkelijke oplossing voor patiënten met een positieve test. Aan deze optie zijn echter nadelen verbonden, namelijk: 1) patiënten zullen ook voor een coronaire revascularisatie operatie een verhoogd risico hebben hoewel angioplastie in bepaalde gevallen uitkomst kan bieden; 2) de positief voorspellende waarde, zoals bij de meeste "stress" onderzoeken is laag wat een extra belasting zal geven voor het coronair revascularisatie programma ten einde een gering aantal complicaties te voorkomen en 3) de mogelijke langere overleving na een revascularisatie is gebaseerd op patiëntengroepen van andere samenstelling dan diegene die een vaatoperatie ondergaan, namelijk een jongere leeftijd, vaker van het vrouwelijke geslacht en minder bekend met vaatziekten.

Een alternatieve behandeling bij hoog-risicopatiënten kan in geselecteerde groepen een angioplastie zijn eventueel gecombineerd met een intravasculaire "stenting" in plaats van een vaatoperatie.

De meest aantrekkelijke behandeling voor patiënten met een hoog risico is een aangepaste perioperatieve begeleiding, maar de vraag is welke therapie in staat is de perioperatieve morbiditeit te verminderen. Behandeling met medicijnen is attractief: dit is snel uitvoerbaar, geen uitstel voor de vaatoperatie noch kans op complicaties tijdens de wachttijd op een coronair revascularisatie operatie, waarbij waarschijnlijk beta blokkers het middel van keuze zijn gezien de pathofysiologie van myocard ischemie gedurende operatie. Slechts 13% van de patiënten geselecteerd voor een vaatoperatie gebruiken reeds beta blokkers, gelijk verdeeld over patiënten met een positieve en negatieve stress test. Gedurende operatie zal een kort werkende beta blokker, zoals esmolol met een halfwaarde tijd van 9 minuten, de voorkeur hebben. Recente studies tonen de veiligheid en effectiviteit van esmolol aan gedurende operatie. Na operatie kunnen beta blokkers nog een beschermende werking hebben wanneer er een verbeterde inspanningsmogelijkheid is als resultaat van de chirurgische therapie. Bij contra indicaties voor beta blokkers kunnen calcium antagonisten gebruikt worden.

Ten einde deze hypothese te evalueren is de volgende stap in ons onderzoek naar de klinische toepassingen van dobutamine-atropine stress echocardiografie, een studie waarbij patiënten die een electieve vaatoperatie ondergaan en een positieve stress test hebben, in twee groepen verdeeld worden, namelijk conventionele behandeling (perioperatief nitroglycerine) versus een additionele behandeling met beta blokkers. In deze studie zal naast de perioperatieve morbiditeit en mortaliteit ook de late cardiale complicaties moeten worden bestudeerd gedurende zo'n drie jaar teneinde een uitspraak te kunnen doen over de beschermende werking van beta blokkers in de peri- en postoperatieve periode.

DANKWOORD

Het was voor mij een voorrecht dit promotie onderzoek te mogen doen. Het in dit proefschrift beschreven onderzoek is tot stand gekomen in samenwerking met de afdelingen Heelkunde, Cardiologie en Interne Geneeskunde. De warme belangstelling voor wetenschappelijk onderzoek op de afdeling Heelkunde heeft sterk bijgedragen aan de verschijning van deze dissertatie. Op deze plaats wil ik graag mijn dank betuigen aan diegenen die mij gestimuleerd hebben dit proefschrift te voltooien.

Dit betreft in de eerste plaats mijn promotor Hero van Urk, wiens steun en vertrouwen de basis hebben gelegd voor dit onderzoek.

Het is Paolo Fioretti geweest die de toepassing van "stress echocardiografie" zag bij patienten die een vaatoperatie moesten ondergaan. Jouw enthousiasme en oprechte vriendschap zijn essentieel geweest voor dit onderzoek.

De hulp van Eric Boersma voor de statistische berekeningen zijn in het gehele proefschrift te vinden.

Arie Man in 't Veld was altijd bereid resultaten te bespreken, zijn eigenschap om een heel artikel in enkele woorden samen te vatten had altijd een ontnuchterende werking, waar ik veel van heb geleerd.

Lies, jouw invloed heeft niet alleen tot mijn opleiding bijgedragen maar ook tot dit wetenschappelijk werk.

Paul Wilson, bij jou heb ik de eerste schreden op het gebied van onderzoek gezet. Jouw discussies en hulpvaardigheid voor het corrigeren van artikelen zijn van grote waarde geweest.

Jos Roelandt, als hoofd van het Thoraxcentrum heb jij mij de mogelijkheid gegeven dit onderzoek te doen. De plezierige ondersteuning van de medewerkers van jouw afdeling hebben tot grote voortgang in het ondezoek geleid.

Ian Thomson, it was your idea to do a study on preoperative cardiac risk stratification in patients scheduled for major noncardiac vascular surgery. The study published in "Circulation" was the first result and will be the base of future studies.

De verpleging van de afdeling 9 Zuid voor het vervoeren van patiënten naar de "stress kamer" op steeds wisselende tijdstippen.

De medewerkers van de afdeling echocardiografie, met name Wim Vletter en Yvonne van 't Zelfden.

De artsen van de afdeling Cardiologie, in het bijzonder Tamas Forster, Jan Hein Cornel, Rosi Arnese, Peter Nierop, Said El-Said en Rob Breedveldt die altijd bereid waren een "echo" er tussen door te doen.

Bas van der Boorden voor het ontwikkelen van de "database" en Joyce Postema voor de administratieve ondersteuning.

Peter Paul Kint voor het "aanscherpen" van de dia's zodat de boodschap nog beter overkwam.

De computer groep verzorgde op uitstekende wijze dia's en figuren, waarvoor ook mijn hartelijke dank.

CURRICULUM VITAE

The author of this thesis was born in 1956 in Rotterdam. After completing secondary school (Athenaeum B) he graduated in 1981 at the Medical Faculty of the Erasmus University of Rotterdam. During a 18 month period he served as a medical officer at the Hague. From 1983 till 1988 he was resident at the Department Internal Medicine I (head Prof. Dr J. Gerbrandy and Prof. Dr M.A.D.H. Schalekamp). In 1989 he was resident at the Department of Clinical Microbiology (head Prof. Dr M.F. Michel). Since 1990 he is working at the Department of Surgery as a consultant internal medicine.