AORTIC STENOSIS: Diagnostic Use and Hemodynamic Effects of Dipyridamole

Akademisk avhandling

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Peter Rask
leg. läkare

Fakultetsoppponent
Med dr Lars-Åke Brodin
Institutionen för Kirurgi
Karolinska Sjukhuset
Stockholm

Umeå 1995
Aortic Stenosis: Diagnostic Use and Hemodynamic Effects of Dipyridamole

Peter Rask, Departments of Clinical Physiology and Internal Medicine, Umeå University, 901 85 Umeå, Sweden

Valvular aortic stenosis is today the most frequently occurring heart valve lesion in the adult Western population. The degree of outflow obstruction, the presence and severity of accompanying valve lesions as well as left ventricular function can be assessed noninvasively using echocardiography - including Doppler, 2-D and colour flow imaging. As concomitant coronary artery disease has significant impact on patient management, coronary angiography is usually performed as a part of the preoperative evaluation. Reliable noninvasive methods for determination of the presence or absence of coronary artery disease would be valuable and may reduce the need for coronary angiography in these patients.

In a total of 129 adult patients with aortic stenosis dipyridamole was infused intravenously (0.56 mg/kg dipyridamole dissolved in 250 ml of saline given over a 4 minute period). There were no serious adverse effects. Patients were examined using cardiac catheterisation, echocardiography, ²⁰¹Tl SPECT and coronary angiography. No patient was excluded due to severe aortic stenosis. The smallest aortic valve area observed was 0.3 cm² and the average valve area was approximately 0.7 cm² in all studies.

During a dipyridamole stress test with the subject in the supine position, patients with aortic stenosis increased their cardiac output, stroke volume, left ventricular work and myocardial oxygen demand and showed a slight drop in blood pressure. Infusion of dipyridamole according to the present protocol appeared to be safe and may be used as a diagnostic tool in patients with aortic stenosis.

The aortic valve area has been considered to be essentially independent of transvalvular flow. However, in the present study both invasive and noninvasive measurements of the size of the valve area were found to be flow dependent. Increases in valve areas of up to 24 % were observed with increased transvalvular flow. This flow dependency of the aortic valve area has to be considered in clinical situations with altered transvalvular flow.

The present study establishes the gender specific normal distribution of ²⁰¹Tl uptake in patients with aortic stenosis given dipyridamole to increase coronary blood flow. Prospective computer assisted evaluation showed a high sensitivity (100%), specificity (75%), and positive (94%) and negative (100%) predictive values for significant coronary artery stenoses in men using the mean - 2.5 SD curve as the discriminating threshold. In women, however, this method showed a considerably lower diagnostic accuracy.

In patients with aortic stenosis increased myocardial oxygen demand is likely to be an important factor for development of wall motion abnormalities when dipyridamole is used in echocardiography stress testing. Using 2-D echocardiography and the combined criteria of a segmental wall motion abnormality at baseline or a new segmental wall motion abnormality after dipyridamole administration as a sign of coronary artery disease resulted in a high sensitivity for detection of multivessel or left anterior descending coronary artery disease (94%).
AORTIC STENOSIS: DIAGNOSTIC USE AND HEMODYNAMIC EFFECTS OF DIPYRIDAMOLE

by

Peter Rask

1995
I rörelse

Den mätta dagen, den är aldrig störst.
Den bästa dagen är en dag av törst.

Nog finns det mål och mening i vår färd —
men det är vägen, som är mödan värd.

Det bästa målet är en nattlång rast,
där elden tänds och brödet bryts i hast.

På ställen, där man sover blott en gång,
blir sömnen trygg och drömmen full av sång.

Bryt upp, bryt upp! Den nya dagen gryr.
Oändligt är vårt stora äventyr.

Karin Boye
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<tr>
<td>2-D</td>
<td>Two-dimensional</td>
</tr>
<tr>
<td>ALVSWI</td>
<td>Aortic left ventricular stroke work index ((J \times \text{beat}^{-1} \times (m^2 \text{BSA})^1))</td>
</tr>
<tr>
<td>AoPmean</td>
<td>Mean pressure in ascending aorta (mmHg)</td>
</tr>
<tr>
<td>AS</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>AVA</td>
<td>Aortic valve area ((cm^2))</td>
</tr>
<tr>
<td>AVAcont</td>
<td>Aortic valve area calculated according to the continuity equation ((cm^2))</td>
</tr>
<tr>
<td>AVAGorlin</td>
<td>Aortic valve area calculated according to the Gorlin equation ((cm^2))</td>
</tr>
<tr>
<td>BSA</td>
<td>Body surface area ((m^2))</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output ( (l \times \text{min}^{-1}))</td>
</tr>
<tr>
<td>ET</td>
<td>Ejection time ((s))</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate ((\text{beat} \times \text{min}^{-1}))</td>
</tr>
<tr>
<td>LVOTarea</td>
<td>Left ventricular outflow tract area</td>
</tr>
<tr>
<td>LVsm</td>
<td>Mean left ventricular systolic pressure obtained by planimetry of the area under the left ventricular pressure curve during ejection ((mmHg))</td>
</tr>
<tr>
<td>LVSWI</td>
<td>Left ventricular stroke work index ((J \times \text{beat}^{-1} \times (m^2 \text{BSA})^1))</td>
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<tr>
<td>NLVSWI</td>
<td>Net left ventricular stroke work index ((J \times \text{beat}^{-1} \times (m^2 \text{BSA})^1))</td>
</tr>
<tr>
<td>n.s.</td>
<td>Not significant</td>
</tr>
<tr>
<td>NYHA</td>
<td>Functional class according to the New York Heart Association</td>
</tr>
<tr>
<td>PTM</td>
<td>Pressure time per minute ((mmHg \times s \times \text{min}^{-1}))</td>
</tr>
<tr>
<td>ΔP</td>
<td>Pressure difference (\text{mmHg})</td>
</tr>
<tr>
<td>ΔPmean</td>
<td>The mean pressure difference between the left ventricle and the aorta during ejection (\text{mmHg})</td>
</tr>
<tr>
<td>ΔPpeak</td>
<td>The peak pressure difference between the left ventricle and the aorta during ejection (\text{mmHg})</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SI</td>
<td>Stroke index ((ml \times \text{beat}^{-1} \times (m^2 \text{BSA})^1))</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke volume ((ml))</td>
</tr>
<tr>
<td>SVRI</td>
<td>Systemic vascular resistance index ((\text{mmHg} \times l^{-1} \times \text{min} \times m^2 \text{BSA}))</td>
</tr>
<tr>
<td>201TI</td>
<td>Thallium-201</td>
</tr>
<tr>
<td>V</td>
<td>Velocity ((m \times s^{-1}))</td>
</tr>
<tr>
<td>VOC</td>
<td>Vitium organicum cordis</td>
</tr>
<tr>
<td>VTI</td>
<td>Velocity time integral ((cm))</td>
</tr>
<tr>
<td>VTias</td>
<td>Velocity time integral across the stenotic aortic valve ((cm))</td>
</tr>
<tr>
<td>VTILVOT</td>
<td>Velocity time integral measured in the left ventricular outflow tract ((cm))</td>
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</table>
ABSTRACT

Valvular aortic stenosis is today the most frequently occurring heart valve lesion in the adult Western population. The degree of outflow obstruction, the presence and severity of accompanying valve lesions as well as left ventricular function can be assessed noninvasively using echocardiography - including Doppler, 2-D and colour flow imaging. As concomitant coronary artery disease has significant impact on patient management, coronary angiography is usually performed as a part of the preoperative evaluation. Reliable noninvasive methods for determination of the presence or absence of coronary artery disease would be valuable and may reduce the need for coronary angiography in these patients.

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During a dipyridamole stress test with the subject in the supine position, patients with aortic stenosis increased their cardiac output, stroke volume, left ventricular work and myocardial oxygen demand and showed a slight drop in blood pressure. Infusion of dipyridamole according to the present protocol appeared to be safe and may be used as a diagnostic tool in patients with aortic stenosis.

The aortic valve area has been considered to be essentially independent of transvalvular flow. However, in the present study both invasive and noninvasive measurements of the size of the valve area were found to be flow dependent. Increases in valve areas of up to 24 % were observed with increased transvalvular flow. This flow dependency of the aortic valve area has to be considered in clinical situations with altered transvalvular flow.

The present study establishes the gender specific normal distribution of $^{201}$Tl uptake in patients with aortic stenosis given dipyridamole to increase coronary blood flow. Prospective computer assisted evaluation showed a high sensitivity (100%), specificity (75%), and positive (94%) and negative (100%) predictive values for significant coronary artery stenoses in men using the mean - 2.5 SD curve as the discriminating threshold. In women, however, this method showed a considerably lower diagnostic accuracy.

In patients with aortic stenosis increased myocardial oxygen demand is likely to be an important factor for development of wall motion abnormalities when dipyridamole is used in echocardiography stress testing. Using 2-D echocardiography and the combined criteria of a segmental wall motion abnormality at baseline or a new segmental wall motion abnormality after dipyridamole administration as a sign of coronary artery disease resulted in a high sensitivity for detection of multivessel or left anterior descending coronary artery disease (94%).
This thesis is based on the following publications, which will be referred to by their Roman numerals.


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INTRODUCTION

The relative frequency of different valve lesions in the western population has changed during the last decades. The decline of rheumatic fever has led to a reduction in the prevalence of mitral stenosis, while the increasing longevity of the general population has led to an increase in the prevalence of aortic stenosis. Valvular aortic stenosis is now the most frequent valve lesion in the adult population [Hall 1989]. The prevalence of at least moderate stenosis in a population between 55 and 86 years of age showed to be approximately 5% in a recent study [Lindroos et al 1993]. The most common aetiologies are congenital malformations and degenerative calcific disease, while rheumatic disease is now a rare cause of aortic stenosis.

Regardless of aetiology, calcification of the valves occurs in most longstanding cases. The expression congenital aortic stenosis is used when there is an obstruction at birth, but excludes cases with malformations of the valves without obstruction. Consequently, malformation of the valves at birth (usually bicuspid) with later development of stenosis is classified as calcified aortic stenosis.

The exact mechanism of obliteration and calcification is not fully understood. Tension, trauma to and turbulence around the malformed valves are thought to play important roles. Infections affecting the valves with organisation of micro-thrombus may also be involved in the aetiology of calcification [Hall 1989]. It has recently been suggested that immune reactions against antigens in the aortic valve leaflets may be crucial to the formation of valvular fibrosis and subsequent calcification [Olsson et al 1994].

The prognosis of aortic stenosis is good as long as there are no symptoms [Pellikka 1990]. After the onset of symptoms however, the prognosis is poor and the mortality rate is higher than in many malignant neoplasms [Rahimtoola 1989]. The time from onset of symptoms to the time of death is approximately 2 to 5 years [Selzter 1987, Braunwald 1988].

Angina pectoris is more common in aortic than in other valve lesions [Olofsson et al 1985] and it has been reported to occur in 40 to 70% of adults with aortic stenosis. Only half of these patients, however, have coronary artery disease [Exadactylos et al 1984]. Syncope is present in about 25% of patients with symptomatic aortic stenosis [Hall 1989]. Dyspnea has been reported as the most frequent symptom (up to 80%) [Cullhed 1964, Nylander et al 1986]. However, severe dyspnea is a late symptom and associated with poor left ventricular function and a poor prognosis [Selzter 1987, Braunwald 1988, Hall 1989].

No medical treatment has yet been found for aortic stenosis. Open heart surgery with replacement of the aortic valve is the treatment of choice. Balloon valvuloplasty has been tried in patients with calcified aortic stenosis. Although temporary hemodynamic improvement can be achieved, the long-term results are not overwhelmingly positive and therefore the use of valvuloplasty in the treatment of aortic stenosis is controversial [Selzter 1987, Hall 1989, McKay 1991].

Although the prognosis of untreated aortic stenosis is poor after the onset of symptoms, prognosis can be improved dramatically by
surgical treatment. Perioperative mortality varies between 2 and 5% in patients without frank left ventricular failure, and the 5-year postoperative survival rate is 85 to 90%. Even in an elderly population, surgical treatment improves prognosis and the quality of life [Braunwald 1988, Lindblom et al 1990, Olsson 1994]. In general, surgery is advisable when the patient has symptoms attributable to the valve lesion. However, patients in whom objective measurements indicate severe stenosis may be asymptomatic, while patients with symptoms which could be attributed to aortic stenosis may have only a mild stenosis according to objective measurements [Hall 1989, Danielsen et al 1991].

Patients with aortic stenosis are routinely examined noninvasively with echocardiography. Echocardiography – including Doppler, 2-D and colour flow imaging – makes it possible to determine the degree of valvular stenosis, the presence and severity of concomitant valve lesions as well as left ventricular function [Skjærpe et al 1985, Helmcke et al 1987, Karp et al 1989, Holm et al 1992].

In adults, the aortic valve area is normally ≥ 3.0 cm² [Greenberg 1987]. Different criteria have been used to define severe aortic stenosis. An aortic valve area of ≤ 0.75 cm² is generally considered to indicate severe stenosis which is likely to produce symptoms. An obstruction of this degree has also been considered as a limit for intervention [Braunwald 1988]. In the presence of normal cardiac output and normal flow across the aortic valve, a peak to peak gradient across the valve of 50 mmHg has also been considered a limit for intervention [Rahimtoola 1989]. Regardless of which criteria are used, the obtained measurements must be interpreted together with the clinical presentation.

While transvalvular pressure differences are dependent upon transvalvular flow, the valve area is considered to be essentially independent of flow. There is, however, evidence that the valve area calculated by the Gorlin equation increases with increasing flow [Bache et al 1971]. The Gorlin equation gives an estimate of the anatomical valve area and contains an empirical constant, which may have different values at different flow rates [Cannon et al 1985]. This could explain the apparent increase in valve area with increasing flow. Another possibility is that the valve area actually increases with increased flow [Burwash et al 1994].

The prevalence of coronary artery disease increases with increasing age and is relatively common in an elderly population with aortic stenosis. As the presence of coronary artery disease has significant impact on patient management, coronary angiography is usually performed as part of the preoperative evaluation. A beneficial effect of simultaneous valve replacement and coronary by-pass grafting in patients with aortic stenosis and coronary artery disease has been reported [Czers et al 1988, Jones et al 1989], and by-pass grafting of hemodynamically significant coronary lesions should be done together with valve replacement. Coronary angiography, however, involves a significant cost and also a small risk for catheterization complications. Reliable noninvasive methods for determining the presence or absence of coronary artery disease may reduce the need for coronary angiography in these patients.
Dipyridamole is frequently used in pharmacological stress testing. It is a potent vasodilator in most vascular beds [Sollevi et al 1984]. Dipyridamole causes near maximal dilatation of the coronary arteries and increases the coronary blood flow in vessels without coronary artery disease [Gould et al 1978]. The dilation of coronary arteries can lead to steal phenomena [Flameng et al 1974]. The exact mechanisms behind the effects of dipyridamole are as yet unknown. Dipyridamole delays inactivation of adenosine [Pfleger et al 1969] and inhibits cellular uptake of adenosine [Knabb et al 1984]. An increased plasma concentration of adenosine is thought to be responsible for the main effect on coronary blood flow. This effect can be blocked by an adenosine antagonist, e.g. theophylline [Sollevi et al 1984].
AIMS

The present series of investigations were undertaken

— to examine hemodynamic changes during a dipyridamole stress test in patients with aortic stenosis and to assess the safety of the procedure,

— to determine whether or not the aortic valve area in patients with aortic stenosis varies with transvalvular flow, and

— to examine if noninvasive methods, dipyridamole $^{201}$Tl SPECT and/or dipyridamole 2-D echocardiography, can demonstrate the presence or absence of concomitant coronary artery disease in patients with aortic stenosis.
All patients included in the present series of studies were adults, between 44 and 80 years of age (mean 68 years), and referred for consideration for aortic valve replacement due to aortic stenosis. A total of 129 patients were examined. The patients were in functional class II, III or IV according to the NYHA classification, with the overwhelming majority in functional class III. The prevalence of angina on effort was approximately 70%. General exclusion criteria were obstructive lung disease, other hemodynamically predominant valve lesions, e.g. mitral insufficiency, aortic insufficiency or mitral stenosis. No patient was excluded due to severe aortic stenosis. The smallest aortic valve area observed was 0.3 cm² and the average valve area was approximately 0.7 cm² in all studies.

Study I.
Six men and four women.

Study II.
Sixteen men and eighteen women.

Study III.
Twenty-eight men and twenty-four women.

Study IV.
Fifty-seven men and fifty-two women.

Study V.
Twenty-three men and twenty females.

Figure 1. Schematic illustration of patients participating in the different studies.
**METHODS**

*Pharmacological stress (Studies I-V)*

In all patients a low dose dipyridamole protocol was used. Dipyridamole (0.56 mg/kg body weight dissolved in 250 ml saline) was infused intravenously over a 4 minute period with the patients in a supine position [Younis et al 1990]. No additional stress was used. Four to 8 minutes after completion of the dipyridamole infusion, 115 mg theophylline was administered slowly intravenously to all patients to reverse the dipyridamole effect.

*Cardiac catheterization (Study I)*

Right heart catheterization was performed using a 7F thermodilution catheter. Left heart catheterization was performed via the femoral artery using a 8F dual port high fidelity catheter allowing simultaneous recording of left ventricular and ascending aortic pressures. The pressure recordings were traced using a digitizing tablet interfaced with a Macintosh computer, allowing calculation of pressure differences.

The equation

\[ p_1 - p_2 = \frac{1}{2} \rho \left( v_2^2 - v_1^2 \right) + \rho \oint \frac{dv}{dt} ds + \Delta pf \]

was presented by Daniel Bernoulli in 1738. Using the "simplified Bernoulli equation", equation 1, instantaneous pressure differences were transformed into velocities [Hatle et al 1980]. Systemic vascular resistance index was calculated using equation 2, and left ventricular stroke work index using equation 3. Pressure time per minute (an index of myocardial oxygen demand) was calculated by equation 4 [Yang et al 1978]. Equations 5 and 6 were derived for comparison between the work required to overcome the resistance of the aortic stenosis and the net left ventricular work (LVSWI = NLVSWI + ALVSWI). Aortic valve area was calculated according to Gorlin and Gorlin, equation 7 [Gorlin & Gorlin 1951], and according to the continuity equation, equation 8 [Skjerpe et al 1985].

<table>
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<tr>
<th>Equation</th>
<th>Expression</th>
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<tr>
<td>Equation 1.</td>
<td>( \Delta P ) = 4.0 \times V^2</td>
</tr>
<tr>
<td>Equation 2.</td>
<td>SVRI = AoPmean x CO(^{-1}) x BSA</td>
</tr>
<tr>
<td>Equation 3.</td>
<td>LVSWI = SI x LVsm x 0.0136 x 9.8 x 1000(^{-1})</td>
</tr>
<tr>
<td>Equation 4.</td>
<td>PTM = LVsm x ET x HR</td>
</tr>
<tr>
<td>Equation 5.</td>
<td>ALVSWI = SI x ( \Delta P_{mean} ) x 0.0136 x 9.8 x 1000(^{-1})</td>
</tr>
<tr>
<td>Equation 6.</td>
<td>NLVSWI = SI x (LVsm - ( \Delta P_{mean} )) x 0.0136 x 9.8 x 1000(^{-1})</td>
</tr>
<tr>
<td>Equation 7.</td>
<td>AVAGor = SV x (ET x 44.3 x ( \Delta P_{mean} )^{1/2}) (^{-1})</td>
</tr>
<tr>
<td>Equation 8.</td>
<td>AVACont = SV x VTIAS(^{-1})</td>
</tr>
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Echocardiography (Studies II-V)

The presence and severity of concomitant aortic or mitral regurgitation was assessed using colour flow imaging. Left ventricular wall motion was assessed using 2-D echocardiography. Myocardial mass was calculated according to the cube formula of Troy [Troy et al 1972]. A myocardial mass index >150 and >120 g/m² in men and women, respectively, was regarded as a sign of myocardial hypertrophy [Levy et al 1987]. Aortic valve area was calculated using the continuity equation,

$$AVA = \frac{VT_{ILVOT}}{VT_{IAS}} \times LVOT_{area} \times e_{VTI}^{-1}.$$

In Study II the flow and valve area were calculated before and during pharmacological stress with dipyridamole. The percent change in flow was calculated as the percent change in $VT_{ILVOT}$ divided by the ejection time from baseline to the post-dipyridamole study. The ejection time was measured as the interval between the onset and end of the transvalvular flow recorded by Doppler. The percent change in valve area was calculated as the change in the fraction $VT_{ILVOT}/VT_{IAS}$ from baseline to the study immediately after dipyridamole.

In Study V, extended evaluation of wall motion abnormalities was undertaken before and during dipyridamole. Left ventricular wall motion was assessed using a 16 segment model [American Society of Echocardiography Committee on Standards 1989]. Depressed wall motion at baseline in at least one segment or a new segmental wall motion abnormality after dipyridamole was considered to indicate the presence of significant coronary artery disease.

Thallium-201 SPECT (Studies III and IV)

Two minutes after the pharmacological stress with dipyridamole, 74 MBq $^{201}$Tl was injected intravenously. Image acquisition started within 10 minutes of the injection of $^{201}$Tl. The images were acquired on a Gamma 11 computer system and tomographic reconstructions were performed. The reconstructed short axis images were transferred to a Macintosh II computer for further evaluation. One basal, one mid-ventricular and one apical short-axis slice were selected manually. For each selected slice the outer boundary of the myocardium was defined by the operator. Starting at the “3 o’clock” position and moving clockwise the computer program divided the slice into 6° segments and the highest activity in each segment was normalised to the highest activity in any segment in the slice (Figures 2 and 3). The relative activity in each segment was then plotted. Vascular territories were assigned for each slice as follows: The 147°-315° segment was assigned to the left anterior descending coronary artery (LAD), the 316°-63° segment was assigned to the left circumflex coronary artery (LCX) and the 64°-146° segment to the right coronary artery (RCA).

Coronary angiography (Studies I-V)

Coronary angiography was performed in all patients via the femoral artery according to Judkins, with multiple angulations and amplification technique. A visually judged area reduction of at least 75% in at least one of the major coronary arteries or in a major branch was considered as a significant
coronary lesion. An area reduction of at least 75% in the main stem was considered as 2-vessel disease, regardless of the presence or absence of stenoses in the left anterior descending or the left circumflex coronary artery.

**Statistics**

Linear regression analyses were performed and Student's two-tailed paired and unpaired t-tests were used where appropriate. In all statistical tests, the null hypothesis was rejected at the 5% level (p<0.05).

**Figure 2.** Quantitative analysis techniques. After operator determination of the outer boundary of the myocardium, the computer divided the cardiac image into sixty 6° segments and the maximum activity within each segment was measured.

**Figure 3.** Thallium-201 distribution for the short-axis slice in Figure 2.
RESULTS AND DISCUSSION

Hemodynamic effects of dipyridamole

The dipyridamole infusion caused a significant increase in heart rate and a decrease in both systolic and diastolic blood pressure. This was observed in all studies. In Study IV, which involved 109 patients, there was an increase in heart rate from a mean of 68 (SD 13) beats/min to a mean of 82 (SD 13) beats/min (p <0.001) and a decrease in systolic and diastolic blood pressure from 142 (SD 21) mmHg to 135 (SD 22) mmHg (p<0.001) and from 84 (SD 13) mmHg to 81 (SD 14) mmHg (p<0.001), respectively. There was thus only a slight decrease in blood pressure after the dipyridamole infusion, which means that the influence on cerebral blood flow ought to be minimal as long as the patient remains in the supine position.

Stroke volume and flow increased after dipyridamole in all patients in Study I (thermodilution method) and in 29 out of 34 patients in Study II (echo-Doppler). The hemodynamic response in both studies thus compared favourably (Table 1). After theophylline administration there was no difference in stroke volume or flow compared with baseline (Study I).

More detailed analysis of the hemodynamic changes was possible in Study I where invasive measurements were made. No significant change in left ventricular systolic or end-diastolic pressure was found. A significant decrease in systemic vascular resistance index was found in all patients after dipyridamole, from 44(SD 8.8) to 31(SD 7.0) mmHg x l'1 x min x m'BSA (p<0.01). The systemic vascular resistance increased after theophylline but it did not return to baseline. Left ventricular stroke work index increased after dipyridamole, from 0.83(SD 0.13) to 0.95(SD 0.16) J x beat'1 x m'BSA'1 (p<0.0001). The increase in the left ventricular work was due to increased work to overcome the aortic outflow resistance and due to increased net left ventricular work.

Comparison of the aortic left ventricular stroke work index (the work required to overcome the resistance of the stenotic valve) and the net left ventricular stroke work index (the work required if, hypothetically, there is no pressure gradient across the valve) indicates that, even in patients with severe aortic stenosis, less than one-third of the ventricular work is explained by the resistance over the stenotic valve. The

<table>
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<tr>
<th>Study I</th>
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<th>Study II</th>
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<tr>
<td></td>
<td>Rest</td>
<td>Dipyridamole</td>
<td>Rest</td>
</tr>
<tr>
<td>CO (l x min'1)</td>
<td>4.39(0.80)</td>
<td>5.72(1.12)***</td>
<td>4.26(1.49)</td>
</tr>
<tr>
<td>SV (l)</td>
<td>70(17)</td>
<td>81(17)***</td>
<td>64(23)</td>
</tr>
<tr>
<td>Flow (ml x s'1)</td>
<td>213(54)</td>
<td>241(59)**</td>
<td>224(75)</td>
</tr>
<tr>
<td>ET (s)</td>
<td>0.329(0.042)</td>
<td>0.341(0.038)</td>
<td>0.285(0.035)</td>
</tr>
</tbody>
</table>

Table 1. Means (SD) for hemodynamic parameters in Studies I and II before and after dipyridamole. Statistically significant differences between rest and dipyridamole are indicated (paired t-test: *p≤0.05, **p≤0.01, ***p≤0.001).
Systemic vascular resistance appears to be more important than the resistance over the aortic valve for determination of cardiac output.

There was also a significant increase in pressure time per minute after dipyridamole. Even if it is not possible to calculate the intrinsic left ventricular work with this method, the increase in both left ventricular stroke work index and pressure time per minute clearly suggest an increase in myocardial oxygen demand. However, after theophylline, there was no significant change compared with baseline.

Four mechanisms have previously been suggested to explain dipyridamole's usefulness in stress testing 1. shortened coronary perfusion time, 2. lowering of the coronary perfusion pressure, 3. coronary dilatation, and 4. steal phenomena [Picano 1992]. A fifth important reason could be added in patients with aortic stenosis – increased left ventricular oxygen demand. In previous studies in patients and animals without aortic stenosis, increased myocardial oxygen demand has not been considered a major factor for dipyridamole-induced ischemia [Picano et al 1986, Fung et al 1987].

In Study II there was an increase in $\Delta P_{\text{peak}}$ from 74(29) to 78(29) mmHg ($p<0.05$) and $\Delta P_{\text{mean}}$ from 50(21) to 54(22) ($p<0.01$) when dipyridamole was given. In Study I the transvalvular peak to peak gradient had a tendency to increase (from 52 to 61 mmHg), not statistically significant.

As there were only minor differences in the hemodynamic measurements when baseline data were compared with measurements after theophylline, theophylline appears to be a suitable antidote to dipyridamole also in patients with aortic stenosis. Approximately 35% of the patients reported chest pain or chest tightness during the dipyridamole infusion and approximately 5% reported mild headache. After theophylline the symptoms were relieved in all patients except in a few who were given sublingual nitroglycerin. There were no serious adverse effects.

**Dependence of aortic valve area on transvalvular flow**

In Study I (invasive study) flow and aortic valve area were assessed at baseline, after dipyridamole infusion and after theophylline. In Study II (Doppler study) flow and aortic valve area were assessed at baseline and after dipyridamole. Measurement of stroke volume is critical in the evaluation of AVA. In these studies, two entirely different methods were used, thermodilution and Doppler, which gave very similar results.

In Study I a new methodology was introduced, AVA was calculated not only according to the Gorlin formula but also by application of the continuity equation. The use of the simplified Bernoulli equation to transform velocity into gradients has been validated in a number of studies [Hatle et al 1980, Stamm et al 1984, Berger et al 1984, Hegrenaes et al 1985] and the reverse, the transformation of gradients to velocity, should be equally accurate. When the velocity time integral is obtained, the aortic valve area can be calculated according to the continuity equation, whereby the need for a constant in the equation is eliminated. The effective orifice area is obtained as opposed to the anatomic area, which the original Gorlin equation is considered to estimate.
The aortic valve area was found to be larger after dipyridamole (Table 2). A correlation was found between flow and aortic valve area both in Study I and Study II. However, there was a wide variation of the flow dependence of the stenotic valve area between patients. Some patients showed a large increase in valve area with increased flow while others showed virtually no change at all (Figure 4). One possible explanation is that some stenotic valves are stiffer and less affected by changes in flow than others. It is thus difficult to predict the change in valve area from the change in flow in an individual patient.

In Study II flow decreased after dipyridamole infusion in four patients who all showed a reduction of the AVA. The reduction of flow was presumably caused by induction of myocardial ischemia during dipyridamole.

<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
</tr>
<tr>
<td>AVGorlin</td>
<td>0.75(0.39)</td>
</tr>
<tr>
<td>AVAcont</td>
<td>0.69(0.36)</td>
</tr>
</tbody>
</table>

Table 2. Means (SD) for calculated AVA (cm²) in Studies I and II before and after dipyridamole. Statistically significant differences between rest and dipyridamole are indicated (paired t-test: *p<0.05, **p<0.01, ***p<0.001).

\[ y = 1.10 + 0.56 \cdot x \quad r = 0.72 \]

Figure 4. Patients in Study II. A linear correlation between per cent change in aortic valve area (\% Change AVA) and per cent change in transvalvular flow (\% Change flow) was found (p<0.001).
The severity of a valvular aortic stenosis is often expressed as the size of the valve area. We observed increases in valve areas of up to 24% with increased flow. If a strict limit for severe stenosis (e.g. <0.75 cm²) is used without regard to the hemodynamic situation, the severity of a stenosis can be underestimated in patients with increased transvalvular flow (aortic regurgitation, inotropic stimulation, etc.), while the opposite is true in patients with reduced flow (left ventricular dysfunction, left to right shunt, etc.).

Noninvasive assessment of coronary artery disease.

The purpose of Studies III and IV was to determine whether or not SPECT can be used to detect or exclude CAD.

In Study III the specificity could not be calculated due to the fact that patients with normal coronary angiograms were compared only with patients having both insignificant and significant lesions according to angiography. Specific limits with regard to gender were not used. Nevertheless, the sensitivity for significant lesions was 88% when the lowest relative activity in each segment in the group without CAD was used as the lower limit of normal. The sensitivity was thus in at least the same magnitude as reported previously in small studies using planar imaging in patients with aortic stenosis [Huikuri et al 1987, Aubry et al 1991]. Encouraged by these results, Study IV was initiated.

In Study IV, 10 men and 10 women, none of whom had angiographic signs of coronary artery disease, a history of myocardial infarction, left bundle branch block or localised hypokinesia (echocardiography), were selected as a reference group and the other eighty-nine patients were evaluated prospectively. In both the reference and the prospective groups, 70% of the patients had a history of angina pectoris. The frequency of chest pain provoked by dipyridamole was 15% in the reference group and 35% in the prospective group. The patients in the reference group showed a mean aortic valve area of 0.70 (SD 0.25) cm² compared with 0.75 (SD 0.37) cm² in the prospective group (n.s.). Ninety-one percent of the men and 92% of the women had myocardial hypertrophy. In the prospective group of 89 patients, 19 patients had no angiographic signs of coronary disease, 13 patients had coronary lesions considered non-significant (< 75% area reduction), and 57 patients had significant coronary artery disease (≥75% area reduction).

In the evaluation of scintigraphic data, the mean activity curve, the lower limit of range curve, the mean minus 2 SD and minus 2.5 SD curves in each slice were calculated separately for men and women in the reference group (Figure 5).

For men, the mean-2.5 SD curves yielded a sensitivity of 100% and a specificity of 75%, and positive and negative predictive values of 94% and 100%, respectively (Table 3). Using mean-2.0 SD or the minimum (range) as the lower limit of normal resulted in a decrease in specificity to 50% and 38%, respectively, while the sensitivity remained at 100%.

Evaluation of different vessel territories was done at the mean-2.5 SD level (Table 4). The highest sensitivity (87%) and specificity (83%) were found for lesions in the left anterior descending coronary artery. The
sensitivity was lowest for the right coronary artery, 69%. No attempt was made to adjust for individual variation in coronary anatomy. Patients with non-significant coronary lesions (5 men and 8 women) were evaluated separately. Four of 5 men with coronary lesions with an area reduction of less than 75% fell below the lower limit of normal regardless of whether -2.5 SD, -2 SD or range was used as discriminating thresholds.

Figure 5 The distribution of thallium-201 uptake for the ten men (a-c) and the ten women (d-f) in the reference groups. Figures a and d represents basal planes, b and e the mid-ventricular planes and c and f the apical planes.
### Table 3.

Results obtained when the mean-2.5 SD curves derived from the reference groups was applied prospectively to a new group of patients.

<table>
<thead>
<tr>
<th>Men</th>
<th>Scintigraphy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>100%</td>
<td>75%</td>
</tr>
<tr>
<td>Angiography</td>
<td>+ 34 0</td>
<td>Positive predictive value</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>- 2 6</td>
<td>Negative predictive value</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women</th>
<th>Scintigraphy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>61%</td>
<td>64%</td>
</tr>
<tr>
<td>Angiography</td>
<td>+ 14 9</td>
<td>Positive predictive value</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>- 4 7</td>
<td>Negative predictive value</td>
<td>44%</td>
</tr>
</tbody>
</table>

### Table 4.

Extended evaluation at the mean- 2.5 SD level, with the heart divided into different vessel territories.

<table>
<thead>
<tr>
<th>Men</th>
<th>LAD</th>
<th>Scintigraphy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>87%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>+ 26 4</td>
<td>Positive predictive value</td>
<td>93%</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td></td>
<td>- 2 10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Men</th>
<th>LCX</th>
<th>Scintigraphy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>81%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>+ 21 5</td>
<td>Positive predictive value</td>
<td>78%</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td></td>
<td>- 6 10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Men</th>
<th>RCA</th>
<th>Scintigraphy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>69%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>+ 18 8</td>
<td>Positive predictive value</td>
<td>78%</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td></td>
<td>- 5 11</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women</th>
<th>LAD</th>
<th>Scintigraphy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>47%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>+ 8 9</td>
<td>Positive predictive value</td>
<td>57%</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td></td>
<td>- 6 11</td>
<td></td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Women</th>
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<th>Scintigraphy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>38%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>+ 5 8</td>
<td>Positive predictive value</td>
<td>36%</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td></td>
<td>- 9 12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women</th>
<th>RCA</th>
<th>Scintigraphy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>36%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>+ 5 9</td>
<td>Positive predictive value</td>
<td>56%</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td></td>
<td>- 4 16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It was not possible to find a cut-off point which resulted in high sensitivity and high specificity for the female patients, for whom the diagnostic accuracy of the test was poor. The -2.5 SD curves resulted in a sensitivity of 61% and specificity of 64% (Table 3). Most previous studies with myocardial scintigraphy have been undertaken in men. Myocardial scintigraphy is more difficult to evaluate in women than in men [DePuey et al 1989]. Breast attenuation artefacts are well known. An additional problem in the present study was that the majority of the women were overweight, 56% of them had a body mass index greater than 25 kg/m² and 17% had a body mass index greater than 30 kg/m². The range in body mass index was larger in females (18-44 kg/m²) than in males (17-34 kg/m²). Most likely, this variation in body mass index is associated with a greater variation in attenuation in the female group. The female heart is usually smaller than the male heart, which may also cause interpretation difficulties. In this study more than 90% of the women had myocardial hypertrophy and the left ventricular cavity on the scintigraphic images was usually small. The results in females may be improved by a combination of appropriate attenuation correction, use of a technetium-99m-labelled perfusion agent and EKG-triggered gated acquisition.

Important gender differences may have been overlooked in the past. The need for gender specific reference groups for 201Tl distribution also in patients without aortic stenosis has been acknowledged, but there is a lack of large prospective studies evaluating test performance in women compared to men [Friedman et al 1982, Rabinovitch et al 1986, Eisner et al 1988, Kong et al 1992, Van Train et al 1993, Wenger 1994]. SPECT is performed more often in men than in women even if groups with the same incidence of typical angina and cardiac risk factors are compared [Shaw et al 1994].

Despite the gender difference in test performance, the overall results of dipyridamole single photon emission computed tomography in Study IV in men and women with aortic stenosis compare well with those of previous studies in patients without aortic stenosis [Leppo 1989]. If all 109 patients (48% females) are included in the evaluation, the overall sensitivity is 84% and the specificity is 75%, using -2.5 SD as the discriminating threshold.

In Study V, 2-D echocardiography at rest and after dipyridamole infusion was used to detect CAD (Figure 6). Using the combined criteria of either a segmental wall motion abnormality at base line or a new segmental wall motion abnormality after dipyridamole, the sensitivity for CAD was 85% and the specificity 70%. The sensitivity for single vessel disease was 71% (5/7) and for multivessel disease 92% (12/13). Sixteen of 17 patients (94%) with significant left anterior descending or multivessel disease were detected. All 6 patients with triple vessel disease were correctly identified as having significant coronary lesions.

An exclusion criterion in Study V was suboptimal echocardiographic image quality. This is an inherit limitation of transthoracic echocardiography and thus also a limitation for dipyridamole echocardiography in assessing the presence of coronary artery disease. However, the proportion of patients excluded for this reason should be less than 10%. Patients with suboptimal transthoracic acoustic windows could be examined with transesophageal echocardiography.
A wall motion abnormality at rest is likely to be present in patients with a previous infarction but it may also be present in patients with severe coronary artery disease without previous myocardial infarction. Thus there is a rationale for including not only a new or worsening segmental wall motion abnormality but also a resting segmental wall motion abnormality as a marker for myocardial ischemia, indicating angiographically significant coronary lesions.

**Figure 6 a-d.** End diastolic and end systolic apical 2-chamber views of the left ventricle at baseline and post-dipyridamole in a patient with significant coronary lesions: a) end diastolic baseline, b) end systolic baseline, c) end diastolic post-dipyridamole, d) end systolic post-dipyridamole. Post-dipyridamole there is a new wall motion abnormality in the apical region (denoted by arrows).
In order for dipyridamole echocardiography to be able to detect coronary artery disease, coronary blood flow must be reduced sufficiently enough to produce myocardial ischemia and segmental wall motion abnormalities. This flow reduction may be caused by redistribution of coronary artery blood flow from a stenotic to a nonstenotic vessel [Flameng et al 1974], or by redistribution of blood flow from the subendocardial to the subepicardial region [Picano et al 1986]. Subendocardial to subepicardial steal may be more common in patients with aortic stenosis because of the high intraventricular pressure and left ventricular hypertrophy.

As there is evidence that dipyridamole causes an increase in myocardial oxygen demand in patients with aortic stenosis (Study I), dipyridamole echocardiography may be a more sensitive test in patients with aortic stenosis than in those without. Factors that tend to increase the sensitivity of a test may also decrease the specificity. This can explain the somewhat lower specificity for significant lesions in our patients compared to the specificity in patients without aortic stenosis [Picano et al 1986].

Angiography is the gold standard in defining coronary artery anatomy, but the interobserver variability is a problem, especially in moderately severe lesions [De Rouren 1977]. More important is the fact that coronary angiography gives an estimate of the anatomical narrowing of the arteries but the effect on blood flow is only assumed, and both under- and overestimation of the hemodynamic effect is possible. Coronary angiography has been reported to be a poor predictor of coronary blood flow reserve [White 1984].

The scintigraphic method reflects the relative coronary perfusion reserve and thus gives a functional measure of the hemodynamic significance of a coronary lesion. Also dipyridamole 2-D echocardiography addresses the significance of coronary lesions in a functional manner. Thus, complete agreement between coronary angiography and dipyridamole scintigraphy or 2-D echocardiography cannot be expected. One patient with an insignificant coronary stenosis judged by angiography but with abnormal scintigraphy developed ST-elevation after valve replacement and required reoperation and grafting of the left anterior descending artery.

If SPECT is performed in men with aortic stenosis approximately 50% of the coronary angiographies in this patient group can be avoided. Since SPECT preferably can be performed in outpatients the overall cost of an examination is much less than the cost of an angiographic examination, consequently, the overall cost will be reduced. If 2-D echocardiography is used the cost reduction will be even greater, if the relatively low rate of detection of single vessel right or left circumflex coronary artery disease can be accepted. However, the performance of 2-D echocardiography is highly dependent on the skill of the echocardiographer whereas SPECT evaluation using the present method is almost operator independent.
GENERAL SUMMARY AND CONCLUSIONS

1. During a dipyridamole stress test (0.56 mg/kg dipyridamole dissolved in 250 ml of saline infused and given over 4 minutes) with subjects in the supine position, patients with aortic stenosis increase their cardiac output, stroke volume, left ventricular work and myocardial oxygen demand and show a slight drop in blood pressure. This indicates that dipyridamole infusion according to the present protocol is not likely to impair cerebral blood flow and may be used as a diagnostic tool in patients with aortic stenosis. Intravenous dipyridamole in patients with aortic stenosis seems to be safe and theophylline is a suitable antidote.

2. The size of the aortic valve area is flow dependent. In the present study, increases in valve area of up to 24% were observed with increased transvalvular flow. This flow dependency of the aortic valve area has to be considered in the evaluation of patients with aortic stenosis.

3. The present study establishes the gender specific normal distribution of $^{201}$TI uptake in patients with aortic stenosis using dipyridamole to increase coronary blood flow. Computer assisted evaluation results in high sensitivity, specificity, and positive and negative predictive values for significant coronary artery stenoses in men using the mean-2.5 SD curve as the discriminating threshold. In women, however, this method has a considerably lower diagnostic accuracy. If SPECT is performed as part of the preoperative evaluation, a substantial number of men can be excluded from coronary angiography prior to aortic valve replacement.

4. Using 2-D echocardiography and the combined criteria of a segmental wall motion abnormality at baseline or a new segmental wall motion abnormality after dipyridamole resulted in a high sensitivity for detection of multivessel or left anterior descending coronary artery disease (94%) with a moderate specificity (70%). Patients with a negative test might be excluded from coronary angiography if the relatively low rate of detection of single vessel right or left circumflex coronary artery disease can be accepted. Increased myocardial oxygen demand is likely to be an important factor when dipyridamole is used in echocardiography stress testing in patients with aortic stenosis.
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