ECHOCARDIOGRAPHIC DETERMINATION OF RISK FACTORS FOR LEFT ATRIAL THROMBI IN MITRAL STENOSIS: A MULTIVARIATE ANALYSIS

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Echocardiographic determination of risk factors for left atrial thrombi in mitral stenosis: a multivariate analysis

by

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Declaration

This is to certify that the content of this thesis
is my own work and have not been submitted for a degree
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PREFACE

Transesophageal echocardiography opened up a new world to me in the examination of the mitral valve and its surrounding structures. For the first time the whole of the left atrium and its appendage could be visualized for the presence of left atrial thrombi.

In clinical practice the striking feature of mitral stenosis is its thromboembolic complication which occurs mainly in young people. The affected patients are usually female, in their productive years and incapacitated by stroke. This complication should be prevented at any cost.

To reach this goal I examined possible risk factors for left atrial thrombi in patients with mitral stenosis by echocardiographic means with the belief that prevention is better than cure.

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Soli Deo Gloria.

"What we know is not much; what we do not know is immense"

Pierre Simon Marquis de Laplace (1749-1827)

French Scientist

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CHAPTER 1
INTRODUCTION

Rheumatic heart disease remains a major challenge in South Africa. In 1972 the overall prevalence rate for rheumatic heart disease was found to be 6.9/1000, with a peak rate of 19.2/1000 in black children aged 15-18 years[1]. The mitral valve is involved in 80-85% of patients with rheumatic heart disease and 50% of these patients will develop mitral stenosis[2].

Left atrial trombi are found in about 20% of patients with mitral stenosis[3,4,5]. The association between the presence of left atrial thrombi and the occurrence of systemic arterial embolization was initially suggested by surgery and autopsy studies[6,7,8]. More recently, two-dimensional transthoracic as well as transesophageal echocardiographic studies have confirmed this association[9,10]. The presence of left atrial thrombi was found to be related to a prior embolic event in 70% of patients with mitral stenosis compared to only 23% in those without mitral stenosis[11]. Wood found the prevalence of systemic emboli in patients with mitral stenosis to be 14%, and of those patients 75% had cerebral emboli[2].

Few complications of valvular heart disease can be more devastating than systemic embolism. With little regard for the severity of the underlying valve lesion, a cerebral embolus, in a moment's time, may cripple or kill a previously asymptomatic patient. The mortality due to systemic embolism in mitral valve disease is about 25%, ranging from 15-35% in various series[12,13,14,15]. Second emboli carry an average mortality rate of 42%[16], with one third of recurrences occurring within one month and two

thirds within a year of the first episode[17,18]. Thus, it is important to prevent thromboembolism in these patients.

It has been known for several decades that while mitral valve disease or atrial fibrillation alone may cause embolism the combination of the two is particularly dangerous[19]. It is well recognized that antithrombotic therapy can reduce, although not eliminate, the likelihood of this catastrophe. In most clinics, therefore, patients with the combination of mitral stenosis and atrial fibrillation are treated with anticoagulants, with good, though not invariably successful, protective effect[18,19,20].

There are, however, some puzzling features which have been pointed out in most of the large-scale studies that have been published[18,19,20]. Embolism may occur in cases of mitral stenosis still in sinus rhythm (20% in three series[8,18,21]), or when mitral stenosis is mild, or when there is pure regurgitation, and even when plasma levels of anticoagulant drugs are within the therapeutic range. The risk of thromboembolism also bears no definite relation to the size of the heart as a whole, or to that of the left atrium.

In aproximately one quarter of patients with pure mitral stenosis the ejection fraction and other ejection indices of systolic performance are below normal, most likely resulting from chronic reduction in preload and elevated afterload, the latter related to a chronically depressed output[22]. Regional hypokinesis is common and perhaps caused by extension of scarring process from the mitral valve into the adjacent posterior basal myocardium or by associated ischaemic heart disease[23]. It has long been

postulated that persistent myocardial dysfunction, perhaps by smouldering rheumatic myocarditis, may be responsible for the poor results following surgical treatment of some patients with pure mitral stenosis[24]. Associated ischaemic heart disease may be responsible for myocardial dysfunction[25]. Although the risk of systemic emboli is greater in those with lower cardiac indices, there is no indication as to when anticoagulant therapy should be initiated in patients with pure mitral stenosis and impaired left ventricular function.

The combination of mitral valve disease and atrial inflammation secondary to rheumatic carditis causes (1) left atrial dilatation (2) fibrosis of the atrial wall, and (3) disorganization of the atrial muscle bundles. The third condition leads to disparate conduction velocities and inhomogenous refractory periods. Premature atrial activation, due either to an outomatic focus or reentry, may stimulate the left atrium during the vulnerable period and may thus precipitate atrial fibrillation. Often this is episodic at first, but then it becomes more persistent[26]. Atrial fibrillation per se causes diffuse atrophy of the atrial muscle, further atrial enlargement and further inhomogeneity of refractoriness and conduction; these changes, in turn, lead to irreversible atrial fibrillation[27]. Although there is poor correlation between systemic emboli and left atrial size, left atrial enlargement $\geq$ 4.8 cm in patients with mitral stenosis was found to be a risk factor for left atrial thrombi in an echocardiographic study, even when taking atrial fibrillation and mitral regurgitation into an account[28,29].

Possible risk factors for left atrial thrombi in patients with mitral stenosis are high age, left atrial enlargement, atrial fibrillation, severity of mitral stenosis, presence of mitral regurgitation, left ventricular dysfunction and the presence of spontaneous echo contrast. However, the strength of association of one or a combination of these factors with left atrial thrombi is not yet quite clear. Thus, a multivariate analysis on the different risk factors in a population with a high prevalence of rheumatic heart disease would be of great value to address the following questions:

(a) At what stage does left atrial enlargement plays an independent role in the pathogenesis of left atrial thrombi in patients with mitral stenosis?

(b) Can the severity of mitral stenosis, as measured in our clinical practice, be used as a guideline for
anticoagulant therapy to prevent thrombo-embolism?

(c) Is mildly impaired left ventricular function a risk factor for left atrial thrombi?

Therefore, the purpose of the present study was to investigate risk factors for left atrial thrombi in mitral stenosis, and to identify criteria for anticoagulant therapy to prevent thromboembolism in patients with mitral stenosis.

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CHAPTER 2
MITRAL STENOSIS

2.1 Natural history

Mitral stenosis in adults is almost always the result of postrheumatic inflammatory and degenerative disease that fuses the mitral commissures and thickens the chordae tendinae[1,2,3].

The majority of patients with significant mitral stenosis remains asymptomatic for a varying length of time. Thus, there is a latent period of mitral stenosis, which might be subdivided into two stages : first, the stage of formation of mitral stenosis, and second, the asymptomatic stage of fully developed mitral stenosis[4]. Wood showed that the latent period lasted an average of 19 years, the mean age for the attack of carditis being 12 years, and the mean age at the appearence of symptoms 31 years. From the onset of symptoms to the stage of total disability, an average of 7 years expired[5].

Roberts and Virmani described the anatomic lesion of rheumatic mitral valve disease as a fibrous thickening of the margins of closure[6]. In rheumatic mitral stenosis, diffuse dense leaflet fibrosis, usually with calcific deposits of variable degree and fusion of one or both commissures, contributes to reduced leaflet mobility. The chordae tendinae are commonly thickened, shortened and fused, causing further obstruction to the left ventricular inflow. Repeated episodes of acute rheumatic valvulitis and carditis accelerates this process. Three types of fully developed mitral

stenosis have been recognized: commissural type, with fusion of the commissures and little involvement of cusps or chordae; cuspal type, in which the leaflets are converted into rigid, calcified structures; and chordal type, in which the chordae are fused, thickened and shortened, further contributing to the stenotic mitral valve orifice. Combinations of these types occur commonly. Stenosis worsens over the years at different rates in different individuals. Once thought to represent only continuing rheumatic activity, the progressive leaflet thickening and calcification that typifies advanced stenosis is now viewed as the valvular response to the stress of chronic turbulent flow through a deformed valve. Because this deformity varies, the magnitude of turbulent stress varies. Some valves remain minimally stenotic for many years, whereas narrowing of other valves may progress rapidly, and the valves become seriously obstructed within a few years[4]. In young patients, commissural fusion mostly occurs, and frequently the leaflets are thin and mobile. In the elderly, calcification and thickening of the leaflets and commissures occur, producing a significantly narrowed orifice and a "fish-mouth" appearance.

The consequence of mitral stenosis is a rise in left atrial pressure, which in time elevates pressures in the pulmonary vascular systems and is largely responsible for dyspnoea, the principal cause of disability. Continued raised left atrial pressure leads to left atrial enlargement and atrial fibrillation with a high risk for thromboembolism[5,7,8,9]. Atrial enlargement can also develop as a consequence of atrial fibrillation[10]. Boudoulas et al demonstrated that mitral stenosis is characterized by increased left atrial volumes and decreased left atrial total emptying fraction; the increased left atrial maximal volume overcompensates for the

decreased left atrial total emptying fraction and thus left atrial total emptying volume remains within the normal range or is slightly elevated in patients with mitral stenosis in sinus rhythm at rest. Two factors may account for the decreased left atrial total emptying fraction in patients with mitral stenosis. First the left atrial dilatation and fibrosis present in mitral stenosis and second the obstruction to blood flow during left atrial emptying by the stenotic mitral valve[11].

The left atrial appendage is frequently involved when there is a thrombus in the left atrium; about 50% of the hearts with left-sided intracardiac thrombosis have the thrombus restricted to the atrial appendage. Among 51 cases of mitral stenosis studied at autopsy, Jordan et al reported the presence of left atrial thrombi in 40 patients. In 20 of these cases (50%) the thrombus was restricted to the left atrial appendage, in 14 (35%) thrombi were present in both the left atrial appendage and the left atrium, and in 6 (15%) the thrombus was found only in the left atrium[12]. There are two potential anatomic reasons for the predisposition to thrombus formation in the left atrial appendage. First, the left atrial appendage is a long, narrow chamber with a narrow tip or apex; and second, the inner surface of the left atrial appendage is marked by muscular ridges[13]. Pollick and Taylor assessed the left atrial appendage function by transesophageal echocardiography. They found left atrial appendage thrombus formation in sinus rhythm and atrial fibrillation to be associated with both poor appendage contraction and dilatation[14].

The left atrium and appendage were examined for the presence of spontaneous echo contrast and thrombus in a multiplane transesophageal

echocardiographic study. Minimal and maximal appendage areas were measured, left atrial appendage ejection fraction was calculated and the left atrial appendage blood flow velocity profiles were obtained with pulsed-wave Doppler at the orifice of the appendage. Patients with left atrial spontaneous echo contrast showed a greater incidence of atrial fibrillation, larger left atrial size, smaller left atrial appendage ejection fraction and smaller appendage flow velocities. In patients with mitral stenosis left atrial appendage ejection fraction and appendage flow velocities were smaller in those with spontaneous echo contrast than in those without spontaneous echo contrast. It appears from this study that the higher pressure and volume load in the left atrium of patients with mitral stenosis may contribute to impaired left atrial appendage contractility[15]. However, in a canine study on compliance of left atrium with and without left atrium appendage, Davis et al found the left atrial appendage to be more compliant than the remaining left atrium. Assuming that this relationship remains in vivo, the left atrial appendage may play an augmented role in maintaining haemodynamic function when filling pressures are elevated as seen in mitral stenosis[16].

Thrombus formation in the left atrium may be present in the atrial appendage, in the body of the left atrium, or both. Roberts reported that of more than 1000 necropsy patients with fatal valvular heart disease, only 5% had a thrombus in the body of the left atrium, all of whom had rheumatic mitral stenosis. All patients with a left atrial body thrombus had atrial fibrillation. A left atrial thrombus was not found in any of the 165 necropsy patients with pure mitral regurgitation. Roberts concluded that a thrombus in the body of the left atrium occurs only in patients with

mitral stenosis. A thrombus in the left atrial appendage is common in any low cardiac output state as well as stenotic lesions of the mitral valve[17].

2.2 Thromboembolism in mitral stenosis

Several risk factors for left atrial thrombi and systemic embolism have been examined in the past. A history of systemic embolization does not necessarily indicate the presence of a residual atrial thrombus because an entire fresh clot may be dislodged with embolization. Baker et al reported on mitral valvotomy in 100 patients with mitral stenosis. Previous embolism had occurred in 17 0f their 100 cases, five while in normal rhythm, but at operation in eight of these no thrombus was found in the auricle[18].

Age more than 40 years appears to be a risk factor for both atrial thrombus[19] and systemic embolism[20,21,22,23,24,25,26]. Garvin found atrial thrombi in 18% of patients under age 40, and in 44% of those over age 40[27]. Neilsen et al concluded that when all of the following factors were present, age greater than 40, moderate or severe valve lesion, atrial fibrillation, and moderate or gross enlargement of the left atrial appendage or left atrium, the prevalence of emboli in patients was 42.9% compared to 14.7% if one of the above factors was absent[28]. However, in a recent study in our department age was not found to be a significant predictor of left atrial thrombi in patients with mitral stenosis, although the median age of patients with left atrial thrombi was slightly higher than that of patients without left atrial thrombi[29].

Mitral stenosis is more commonly found in women than in men, and thus the thromboembolic phenomena of mitral stenosis are more frequent in women. Correcting for this bias, there is no additional risk of thromboembolism for either sex[24,27].

The majority of patients with valvular heart disease who have atrial fibrillation have rheumatic mitral valve disease. The increased risk of systemic embolism in patients with rheumatic mitral valve disease complicated by atrial fibrillation is well documented. The incidence of atrial fibrillation has been reported to be 41% in mitral stenosis[5]. Probst et al found a stepwise increase in the incidence of atrial fibrillation with advancing age in mitral stenosis[30]. In the large series of Coulshed et al which included 839 patients with rheumatic heart disease, 8% of patients with predominant mitral stenosis and normal sinus rhythm had emboli compared with 31.5% of patients with atrial fibrillation[31].

Somerville and Chambers concluded that the incidence of systemic embolism is directly related to the size of the left atrium and in particular to the size of the appendage[32]. Several large studies failed to verify this finding[31,33]. Bansal et al examined 148 patients with mitral valve disease for the presence of left atrial thrombi. Of the 13 patients with left atrial thrombi, 11 had mitral stenosis with a left atrial size of 4.8 cm or more. Only 1 patient with mitral stenosis and left atrial thrombi had a left atrial size of 4.0 cm and was in atrial fibrillation[34]. In our echocardiographic study left atrial enlargement, in particular left atrial size $\geq$ 4.8 cm was a risk factor for left atrial thrombi in patients with mitral stenosis[29].

Even though the risk of left atrial thrombi is directly related to the severity of mitral valve disease[12,34,36], no such relationship prevails for systemic embolism[20,22,36]. This discrepancy may be because many of these studies were done in the pre-echocardiographic era and this probably explains the differing results from the different studies.

Casella et al found no correlation between the severity of mitral stenosis and the incidence of systemic emboli. Comparing 21 patients with mitral stenosis and embolism with 36 patients with mitral stenosis without embolism, they found no statistically significant differences with respect to cardiac functional class, left atrial pressure, mitral valve pressure gradient, mitral valve area, left ventricular end-diastolic pressure, mean pulmonary artery pressure or wedge pressure[24]. This finding was not supported by Neilsen et al who concluded that moderate or severe mitral stenosis increased the risk for systemic emboli[28].

Casella et al found an independent relationship between the occurrence of systemic emboli and low cardiac output[24]. However, reviewing the records of 1,600 patients who had been operated on for predominant mitral stenosis, they found no statistically significant difference with respect to functional class or mitral valve area in those with preoperative embolism compared to those without preoperative embolism. Ellis and Harken, reporting on the same group of patients with cardiac surgery, found that operative emboli occurred more frequently in N. Y. Heart Association class IV patients than in class II and III patients (12% compared to 4%)[7]. Graham et al observed that the frequency of arterial embolism was similar in patients with and without heart failure (45% and

57% respectively)[22]. Daley et al found no correlation between the frequency of arterial embolism and the duration or severity of cardiac failure[20]. Finally, Laws and Levine comment that while most of their patients with emboli had experienced heart failure, this failure was generally compensated when the embolism occurred[37]. In summary, clinical and postmortem studies generally show that patients with severe forms of rheumatic heart disease have an increased frequency of atrial thrombosis, but not of systemic embolism.

Coulshed et al found patients with predominant mitral regurgitation to have the same risk of systemic embolism as those patients with predominant mitral stenosis[31]. With dominant mitral stenosis, emboli occurred in 8% of patients with sinus rhythm and in 31.5% of patients with atrial fibrillation. With dominant mitral regurgitation, emboli occurred in 7.7% of patients with sinus rhythm and 22% of patients with atrial fibrillation. They noted that systemic embolism becomes more commoner with increasing age and with atrial fibrillation, presumably because of atrial stasis leading to clot formation in the atrium. This is in contrast to the findings of others that left atrial thrombosis and systemic emboli are primarily associated with predominant mitral stenosis as opposed to regurgitation[2,20,38,39,40,41,42].

Smoke-like echo (spontaneous echo contrast) has been observed in the left atrial cavity in some patients with mitral stenosis[43]. Cardiac chambers and blood vessels are usually echolucent. However, the term spontaneous echo contrast describe a wafting swirling haze that is occasionally seen in great vessels and dilated cardiac chambers under conditions of blood

stasis. Spontaneous echo contrast can be seen in the left atrium of patients with significant mitral stenosis (particularly those with a dilated left atrium and atrial fibrillation) and in the left ventricle and aorta during conditions of low output. The features that define smoke are 1) multiple instances of low amplitude echogenic swirling haze; 2) slow, repetitive movement in the cavity ; and 3) disappearence when blood flow increases, as when blood enters another cavity[44]. Therefore, the believe of Beppu et al that the smoke-like echo is generated in conditions of stasis. This reasoning is also supported by their findings that the smoke-like echo was not demonstrated when the blood was stirred by severe mitral regurgitation and that it disappeared with the elimination of stasis. A condition of stasis might implicate aggregated red blood cells as the possible source of the echo[43].

Red blood cells aggregate to form rouleaux in patients with severe mitral stenosis because of blood flow stasis and decreased shear force; therefore smoke-like echo is observed in the left atrium. When blood flow passes through the stenotic mitral orifice into the left ventricle, flow velocity and shear forces are increased, rouleaux disperse and smoke-like echo disappears. Complete resolution of smoke-like echo in the left atrium has also been shown to follow relief of mitral stenosis after percutaneous balloon mitral valvuloplasty. They postulate that erythrocyte rouleaux are responsible for the smoke-like echo observed in patients with mitral stenosis[45].

In an in vitro model spontaneous echo contrast was visualized only in whole blood and in physiologic concentrations of red blood cells in plasma.

Platelets alone, plasma alone, pletelets and plasma, or very high red blood cell concentrations did not produce spontaneous echo contrast. Merino et al conclude that at physiologic concentrations, a red blood cell and plasma protein interaction was responsible for the production of spontaneous echo contrast. This interaction is platelet independent and shear dependent. Shear stress, which is the product of the velocity gradients between parallel flow lines located in the centre and the periphery of blood vessels times the blood viscosity, exerts a mechanical force on red cell aggregates that overcomes the weak attracting forces, thus maintaining the erythrocyte separation in flowing conditions. Shear rate has been grossly estimated to be as low as 2 to 9 s^{-1} in the left atrium in severe mitral stenosis and in the dilated aneurysmal left ventricle. These extremely low shear conditions may permit red cell aggregation and thus the visualization of blood flow lines known as smoke. This smoke-like echo appears to be closely related to thrombus formation in the left atrial cavity[44].

Yet, Daniel et al in an echocardiographic and haemodynamic study found no significant differences in the cardiac index of patients with and without spontaneous echo contrast. Patients with spontaneous echo contrast had a significantly larger left atrial diameter, and a greater incidence of both left atrial thrombi and a history of arterial embolic episodes, than did patients without spontaneous echo contrast. Transthoracic echocardiography revealed left atrial spontaneous echo contrast in only 1 (0.8%) of the 122 patients; this patient had undergone mitral valve replacement 3 years before the study and the left atrial diameter was 76 mm. In contrast, in the transesophageal echocardiograms, spontaneous echoes within the left

atrium could be detected in 61 (50%) of the 122 patients; they were classified as "marked" in 42 (34.4%) and "mild" in 19 patients (15.6%). Independent evaluation by two observers resulted in only minor discrepancies concerning the classification of marked or mild echo contrast in three patients, amounting to an interobserver variability of 2.5%. There were no differences regarding presence or absence of spontaneous echoes[46]. .Multivariate analysis in 89 patients with mitral stenosis or mitral valve replacement showed that spontaneous echo contrast was the only independent predictor of left atrial thrombus or suspected embolism, or both[47]. Hwang et al concluded that patients with left atrial spontaneous echo contrast had a significantly higher risk for thromboembolism[48].

The relationship between left ventricular ejection fraction and the presence of left atrial thrombi in patients with mitral stenosis has so far not been examined in a large prospective echocardiographic study. However, in a retrospective transesophageal echocardiographic study, mitral stenosis, left ventricular ejection fraction < 25%, and left atrial dilatation ≥ 5.0 cm were found to be independent risk factors for left atrial thrombus formation[49]. The incidence of impaired left ventricular function in patients with isolated mitral stenosis was found to be 29%. This finding is in line with that of others[50,51]. Their data are consistent with patients having (1) systolic dysfunction due to an intrinsic abnormality of contraction or (2) excessive left ventricular afterload, or both, and they could not state with certainty which mechanism was operative. The tendency for embolization correlates inversely with cardiac output. It may be due to a rise in left ventricular end-diastolic pressure

with a resultant decrease in left atrial emptying. This will lead to a further increase in left atrial size and ultimately atrial fibrillation which is the single most important risk factor for the development of left atrial thrombus.

Yamamoto et al found that the coagulation system is activated in the left atrium of patients with mitral stenosis even during anticoagulation. Levels of fibrinopeptide A and thrombin-antithrombin III complex were significantly higher in the left atrium than those in the right atrium and did not correlate with mean transmitral gradient, dimension of the left atrium or reciprocal of the mitral valve area. Their findings also suggest that platelet activity is not significantly increased in the left atrium of these patients[52]. However, Fukuda and Nakamura reported that patients with mitral stenosis, whether presenting with sinus rhythm, atrial fibrillation, or atrial fibrillation and congestive heart failure had diminished antithrombin III levels and increased B thromboglobulin levels, reflecting platelet activation in vivo[53]. To clarify whether the formation of thrombi could be induced by atrial fibrillation itself or by factors predisposing to atrial fibrillation such as mitral stenosis, plasma D-dimer levels were measured in 73 patients with chronic atrial fibrillation and 21 patients without atrial fibrillation. Plasma D-dimer levels were significantly higher in patients with atrial fibrillation compared to those without. In both groups, there were no significant differences in plasma D-dimer levels between patients with and without organic heart disease, suggesting that atrial fibrillation itself may be more important than factors predisposing to atrial fibrillation in the development of intravascular clotting[54].

Dewar and Weightman examined two groups of patients for possible risk factors for systemic embolism, one group of 34 cases of mitral valve disease and 4 cases of lone atrial fibrillation, all of whom had a history of embolism, and also a group of 24 cases of mitral valve disease who had no such history. All patients were on long-term anticoagulant therapy. Comparison of the two groups disclosed no features that would distinguish those who had the greater risk of embolism. Fibrinolytic activity was less and the level of B thromboglobulin was greater than normal in both groups. No positive association was found between cigarette smoking or the use of the contraceptive pill and the risk of embolism[21].

2.3 Echocardiography in the diagnosis and quantification of mitral stenosis

2.3.1 Transthoracic echocardiography

The detection of rheumatic mitral stenosis was the first clinical application of echocardiography. The most specific M-mode echocardiographic sign for mitral stenosis is the diastolic anterior movement of the posterior leaflet which is due to the commissural fusion and the anterior tethering of the posterior toward the anterior leaflet during diastole[55]. Additional M-mode echocardiographic features, other than the mitral valve, can help in the diagnostic evaluation of patients with mitral stenosis. The most important of these extra-valvular findings is the estimation of left atrial as well as left ventricular size. The combination of a thickened mitral valve and an anterior moving posterior leaflet together with an enlarged left

atrium and normal left ventricle allows for a very high accuracy in the echocardiographic detection of mitral stenosis.

The two-dimensional long-axis, short axis and apical four chamber views can be used to image the mitral valve. In the two-dimensional parasternal long-axis view, the arching of the anterior mitral leaflet in diastole is a prominent sign of mitral stenosis[56]. This echocardiographic sign is related to the thickening and immobility of the leaflet tips while maximum mobility in the leaflet's body is maintained, and is associated with the opening snap on auscultation. In patients with heavy calcification of the mitral anterior leaflet's tip and body, the mitral valve arching as well as the opening snap is absent.

The major contribution of two-dimensional echocardiography has been the ability to assess the mitral orifice size by using the short axis view[56,57,58,59,60]. Excellent correlation of echocardiographically measured mitral valve orifice size to that measured at surgery[57], as well as to the area obtained by the Gorlin formula[56,58] at cardiac catherization, has been reported. It seems, however, that in patients with mild to moderate mitral stenosis, mitral valve orifice size determined by two-dimensional echocardiography overestimates the cardiac catherization measurement by 0.2 cm^2. The reason for this discrepancy is that echocardiography uses direct anatomic measurement of the mitral orifice, whereas the haemodynamic estimation is based on mitral valve flow which may be altered by valvular, subvalvular and other factors[59]. Importantly, technical difficulties, such as proper gain settings, echo dropout phenomena, and the timing of the cardiac cycle of mitral orifice

measurement as well as the boundary tracing method, can significantly alter the results.

Henry et al concluded that two-dimensional echocardiography is extremely useful in the evaluation of patients with mitral valve disease because it provides a noninvasive method for directly measuring the mitral valve orifice area that is accurate even in the presence of mitral regurgitation[57] .

Doppler echocardiography is particularly important in quantifying disease severity. Hatle et al[61] described an alternative method based on the time interval needed for transmitral blood flow to reach one half of the transmitral gradient as determined on the Doppler echocardiographic image, the so-called pressure half-time (P1/2T). Using the presure half-time the area of the mitral valve is calculated simply as 220/pressure half-time. Results obtained from this method correlate very well with those of cardiac catherization and are scarcely influenced even by wide variations of the R-R interval characteristics of patients with a concomitant atrial fibrillation. Gonzalez et al found Doppler and two-dimensional echocardiographic quantification of mitral stenosis to be complementary[62]. Ghiringhelli et al suggested the use of two-dimensional echocardiography, or of the Doppler pressure half-time method, to classify correctly patients with mitral stenosis, with the additional suggestion to use both techniques whenever possible[63].

The distinctive two-dimensional echocardiographic features of a left atrial thrombus include a mass of irregular nonmobile laminated echoes within

an enlarged atrial cavity, usually with a broad base of attachment to the posterior left atrial wall or in the left atrial appendage[64].

In summary, M-mode, two-dimensional and Doppler echocardiography provide excellent quantitative and qualitative information in the patient with mitral stenosis. The degree of stenosis, the actual orifice size, the pliability of the leaflets, the degree of calcification as well as the existence of left atrial thrombi are all determined non-invasively. Echocardiography enables follow-up and provides vital information as to the progression of the disease and the possible development of complications.

2.3.2 Transesophageal echocardiography

The risk of thrombus formation and embolic events associated with rheumatic mitral stenosis has been well documented, and has become an accepted aspect of the management of such patients. The presence of left atrial thrombi is considered to be a contraindication to closed surgical mitral commissurotomy and to percutaneous transvenous mitral commissurotomy[65,66]. Two-dimensional echocardiography is useful to detect left atrial thrombi. However, transthoracic echocardiography does not recognize small thrombi resident in the left atrial body. The sensitivity of two-dimensional transthoracic echocardiography for detecting left atrial thrombi ranges from 33-59%, and the specificity is 99%[34,67,68]. To detect left atrial thrombi with high sensitivity and to visualize left atrial appendage thrombi and left atrial spontaneous echo contrast, a

phenomenon related to left atrial stasis, transesophageal echocardiography is needed.

The basic requirement for transesophageal echocardiography is a complete two-dimensional Doppler color flow echocardiographic instrument to which a transesophageal transducer(probe) has been attached. The single plane probe is fitted with a 90-degree horizontal tomographic plane of section, which usually provides adequate visualization of the left atrial appendage. However, biplane(180-degree horizontal tomographic plane) and multiplane(360-degree horizontal tomographic plane) may provide better visualization of the left atrial appendage. The left atrial appendage is imaged in the basal short-axis scan. The left atrial appendage is to the left of the left atrial cavity and appears as a triangular extension. Muscular ridges(pectinate muscles) within the appendage are easily visible and should not be confused with thrombi. The left atrial appendage overlies the left coronary artery. The orifice of this appendage is anterior to the left upper pulmonary vein, and the two are separated by a distinct ridgelike infolding of the wall[69].

Aschenberg et al did a transesophageal study on patients with mitral stenosis resulting in 100% sensitivity and specificity of the technique for detecting left atrial appendage thrombi[70]. In a transesophageal echocardiographic study to detect clots in candidates for percutaneous transseptal mitral balloon valvuloplasty, 26% of the patients revealed a left atrial thrombus. In only one of these patients was there a suspicion of left atrial thrombus on transthoracic echocardiography. It is concluced that transesophageal echocardiography is more sensitive than conventional

echocardiography in detecting left atrial clots. Because of the potential risk of embolization, transesophageal echocardiography is recommended in all candidates for balloon mitral valvuloplasty[71].

In a prospective clinicopathological study in 213 consecutive patients with chronic rheumatic mitral valve disease the diagnostic accuracy of transesophageal echocardiography for detecting left atrial thrombi was 99.1%, with a positive predictive value of 100% and a negative predictive value of 98.9%[72].

Brickner et al did a retrospective analysis on the relation of thrombus in the left atrial appendage by transesophageal echocardiography to clinical factors for thrombus formation. Their results indicated that left atrial enlargement $\geq$ 5.0 cm, severe left ventricular dysfunction (ejection fraction $\leq$ 25%) and mitral stenosis were independent risk factors for the formation of left atrial appendage thrombus. Although transesophageal echocardiography does provide excellent visualization of the left atrial appendage , the technique is not 100% sensitive or specific for the diagnosis of left atrial appendage thrombus. One of the reasons is the pectinate muscles in the wall of the left atrial appendage which is a normal finding that could potentially be confused with thrombus, especially if they are hypertrophied. It has been postulated that fresh thrombi may have acoustic characteristics similar to those of blood and,therefore, may not be detected by transesophageal imaging. Also, the absence of of thrombus in the left atrial appendage at the time of the transesophageal study is not synonymous with an absence of risk for cardioembolism[73].

2.4 Anticoagulant therapy in mitral stenosis

Autopsy studies indicate a high frequency of clinically unrecognized embolism in patients with rheumatic heart disease, suggesting that data derived from clinical reporting may underestimate the true frequency of systemic embolism[74].

Embolization may occur as the first manifestation of mitral stenosis, and may occur in patients without significant cardiac functional impairment. There is consensus that in patients with significant cardiac functional impairment the treatment to prevent recurrence of embolization is surgical; however, when there is little or no cardiac functional impairment, therapy is controversial. Surgical therapy is recommended by some, while long-term anticoagulant therapy without surgery is preferred by others[75,76]. Despite the clear relationship between rheumatic mitral valve disease and systemic embolization, not all studies have demonstrated the efficacy of anticoagulant therapy in reducing embolus-related mortality and morbidity. Szeleky reported a 2.5 times higher risk of recurrence of systemic embolism among a group of patients that were not on anticoagulant therapy compared to patients that were started on warfarin after an initial embolic episode; the incidence of recurrent embolism in patients with mitral valve disease who received warfarin was 3.4% per patient-year, while in the nonanticoagulated group it was 9.6% per patient-year[9]. Adams et al followed up 84 patients with mitral stenosis and cerebral emboli for up to 20 years, half of whom received no anticoagulant therapy (1949-1959), and half of whom received warfarin (1959-1969). Using life-table analyses, a significant reduction in

emboli was reported in the treated group, with 13 deaths from emboli in the untreated group and only 4 deaths in the treated group. The authors concluded that treatment with oral anticoagulants, started immediately after the first embolic episode, appears to decrease mortality during the ensuing 6 months, but they were unable to show longer-term benefits[77]. In another large series, Fleming and Bailey reported a dramatically lower incidence of embolization in patients with rheumatic mitral valve disease that were on anticoagulant treatment when compared with historical control rates. They found a 25% incidence of emboli among 500 untreated patients with mitral valve disease (historic controls), while in 217 patients treated with warfarin only 5 embolic episodes occurred over a 9.5 year period, yielding an incidence of 0.8% per patient-year. On the basis of their findings the authors concluded that all patients with more than trivial mitral valve disease should be considered candidates for long-term warfarin therapy, regardless of such variables as age, cardiac rhythm or left atrial size[30]. The results of a study by Siegel et al showed that the risk of recurrent systemic embolization in patients with mitral stenosis can be markedly reduced by the use of long-term anticoagulation, and are in agreement with previous observations[78].

The natural history of left atrial thrombi in mitral stenosis is not yet fully known. Hung et al reported the resolution of left atrial cavity thrombi observed with transthoracic two-dimensional echocardiography in patients with mitral stenosis after warfarin therapy[79]. They observed incidental resolution of thrombus in the left atrial cavity in two patients with severe mitral stenosis after warfarin treatment for 7 months in one and 1 year in the other. A follow-up study with transesophageal echocardiography was

done on 4 patients with left atrial appendage thrombi. Resolution of the appendage thrombi was demonstrated after 2, 4, 5 and 12 months of warfarin therapy respectively[80]. These findings are very interesting as warfarin is not known to dissolve clot but merely to prevent thrombus formation.

They felt that since the observation was limited to a small number of patients, more study is warranted to further understand the natural history of left atrial thrombus. It is however more than likely that many of these thrombi spontaneously thrombolyse themselves.

Whereas early studies of the efficacy of anticoagulation treatment predominantly involved warfarin or its equivalent, recent attention has focused on the possible role of antiplatelet therapy. Platelet survival has been found to be shortened in some groups of patients with mitral stenosis, and evidence has accumulated to support the hypothesis that patients with significantly shortened platelet survival may more frequently experience systemic embolization[81]. Toy et al have shown a correlating increase of platelet stickiness in patients with thromboembolism[82]. In patients with abnormal heart valves and shortened platelet survival, treatment with sulfinpyrazone, a platelet inhibitor, was found to enhance platelet survival. Steele and Rainwater conducted a prospective, double-blind study of the efficacy of sulfinpyrazone as compared with placebo in prolonging platelet survival and diminishing the incidence of embolization in a cohort of patients with mitral stenosis and shortened platelet survival. The study demonstrated an impressive decrease in the frequency of embolization accompanied by a significant increase in the life span of the group treated with sulfinpyraxone[83]. Although antiplatelet therapy is likely to become

an important substitute for or addition to warfarin treatment in appropriately selected patients, platelet survival tests are not widely available, at least in South Africa, where their use is mainly restricted to academic centres.

Anticoagulation treatment in patients with mitral stenosis implies a balance of two risks: the risk of bleeding due to poorly controlled anticoagulation, against the thrombotic or embolic risk of the condition itself. The incidence of major bleeding complications of warfarin treatment varies between 4.4% and 8.2%. Forfar followed 501 patients receiving anticoagulants for up to 7 years. The incidence of hemorrhagic complications sufficient to require medical advice and treatment was 8.2% and 4.3% per patient-treatment year, respectively. Nearly half of the bleeding episodes were considered potentially life-threatening; in 96% of these events, the prothrombin time was beyond the desired range for the therapeutic ratio of between 1.8 and 2.6 to 1[84]. Unlike several other series[85,86,87], this large study demonstrated no increase in bleeding propensity with advancing age. Although reports of higher rates of bleeding complications are common[88,89], several factors have been identified in the literature as likely to contribute to a lower rate of major problems. Careful follow-up in specialized clinics appears to result in complication rates of 4% or lower[85,90] . For some indications for anticoagulation treatment a reduction in the therapeutic ratio results in fewer complications at no appreciable cost in treatment failures. Thus, Hull et al found no increase in the recurrence of deep venous thrombosis but did note a significant decrease in bleeding complications when the mean prothrombin time was decreased from 19.4 to 15 seconds[91].

Therefore, bleeding on warfarin treatment is not clearly related to the patient's age but correlates positively with the duration of therapy and the degree of anticoagulation.

Although it is frequently stated that prior embolism, the size of the left atrium, and the presence of left atrial thrombi are important prediposing risk factors, only the presence of atrial fibrillation has consistently been proven to be a reliable risk factor for the occurrence of systemic embolism[74,92].

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CHAPTER 3
PATIENTS AND METHODS

3.1 Study Population

In a cross-sectional study, which was approved by the Ethics Committee of the University of the Orange Free State, 146 consecutive patients with predominant mitral stenosis were examined. The patients were 29 males with a median age of 33 years (range 16 to 60 years) and 117 females with a median age of 34 years (range 16 to 67 years). All patients were recruited at the Echocardiography Laboratory at Pelenomi Hospital, Bloemfontein, South Africa between June 1991 and August 1993.

Patients were included in this study if they had a mitral valve area of less than 2.0 cm^2, as shown by transthoracic echocardiography, and were on no anticoagulant therapy. After informed consent was obtained, the patients were scheduled for transesophageal echocardiography for the detection of left atrial thrombi. The transesophageal echocardiographic studies were done by the investigator himself. All patients had a standard 12-lead resting electrocardiogram. The presence of left atrial thrombi in those patients that underwent open-heart mitral valve surgery was confirmed by direct visual inspection of the left atrium and its appendage.

3.2 Echocardiographic investigations

An ATL ultramark 9, two-dimensional, Doppler color flow echocardiographic instrument was used for transthorasic

echocardiography and a monoplanar 5 Mhz transducer at the tip of an adult echoscope was used for transesophageal echocardiography. Studies were performed with a single plane probe because biplane or multiplane probes were not available at the time when the study was planned.

Transthoracic echocardiography was performed using standard views, M-mode, two-dimensional and Doppler echocardiography, for the confirmation and quantitation of mitral stenosis, as well as the determination of left atrial size. Basal left ventricular ejection fraction was measured by two-dimensional echocardiography in the parasternal long-axis view. End-diastolic and end-systolic dimensions were aligned perpendicular to the major axis of the ventricular cavity at the level of the chordae tendinae[1] (Fig. 1). Left ventricular ejection fraction was calculated by using the Teichholtz formula[2].

The left atrium was measured at the aortic valve plane and also perpendicular to the aortic root, utilizing the leading edges of the left atrial posterior wall and the posterior aortic root in the parasternal long axis view[1] (Fig. 2). A left atrium-aorta ratio larger than 1 was taken as enlargement of the left atrium and the absolute values for left atrial size are reported[3].

The mitral orifice area was imaged by two-dimensional echocardiography in the parasternal short axis view. The mitral orifice was imaged during its maximal separation in early diastole and planimetred to measure mitral valve area as described by Henry et al[6] (Fig. 3). In two cases with poor

quality images of the mitral orifice, the mitral valve area was measured by Doppler pressure half-time[7].

Two-dimensional echocardiography was used for the detection of left atrial thrombi. A left atrial thrombus was reported when a well circumscribed echo-reflective mass was noted in 2 or more echocardiographic views[8,9].

Transesophageal echocardiography was done according to the criteria outlined in a Mayo Clinic publication[10]. Patients were examined in the left lateral position, no premedication was given, and they had to abstain from the intake of fluids or food for at least 4 hours before the procedure. The upper pharyngheal region was locally anesthetized with 10% xylocaine spray before introduction of the echoscope.

Transgastric short axis, 4 chamber and basal short axis views were used. Studies were recorded on videotape, and the interpretation was made by the primary operator at the completion of the procedure. Special attention was paid to the left atrium and left atrial appendage for the presence of left atrial thrombi. The left atrial appendage was viewed from the basal short axis, with the tip of the probe slightly flexed to observe the length and breadth of the left atrial appendage (Fig. 4). Mitral regurgitation was graded in the 4 chamber view as absent, mild (abnormal systolic flow confined to area just above mitral valve), moderate (flow extends to proximal one third of left atrium), moderately severe (regurgitant jet detected half way up left atrium) and severe (systolic flow detected beyond mid-left-atrial level), according to the area covered by the Doppler color flow jet[11] (Fig. 5).

Spontaneous echo contrast was graded in the 4 chamber view as absent, mild, and moderate or severe. It was diagnosed if a swirling cloud of echoes was noted in the left atrium. Spontaneous echo contrast was reported as mild if the swirling motion was only visualized in part of the left atrial chamber at a high gain, and it was reported as moderate or severe if the swirling motion covered the whole left atrial chamber at a normal gain control[12,13] (Fig. 6).

3.3 Statistical analysis

3.3.1 Risk factors for left atrial thrombi

The following potential risk factors for left atrial thrombi were investigated: age, sex, rhythm, left atrial size, mitral valve area, spontaneous echo contrast, mitral regurgitation and left ventricular ejection fraction. A list of the potential risk factors is given in Table I. The potential risk factors age, sex, rhythm, left atrial size and mitral valve area were categorized into 2 risk categories (Table I). The potential risk factors spontaneous echo contrast and left ventricular ejection fraction were originally categorized into 3 risk categories, while the risk factor mitral regurgitation was originally categorized into 5 risk categories. As a consequence of the results of the univariate analysis, the 3 risk categories of left ventricular ejection fraction and the 5 risk categories of mitral regurgitation were collapsed into 2 risk categories for each of these risk factors (see sections 4.2.7 and 4.2.8 below, as well as Table I).

Both a univariate and a multivariate analysis of the data were performed.

3.3.2 Univariate analysis

Association between risk factors and left atrial thrombi:

In the univariate analysis, the association between each risk factor and the presence of left atrial thrombi was investigated, one risk factor at a time. The values of risk factors with continuous data, namely age, left atrial size, and mitral valve area were compared for patients with and without left atrial thrombi, respectively, using the nonparametric Mann-Whitney test. The analysis was performed using the SAS procedure NPAR1WAY[14]. The data were summarized through the median and the range, and were analysed nonparametrically, because of the non-Gaussian distribution of the data.

Furthermore, with respect to all risk factors except spontaneous echo contrast, if appropriate after categorisation into 2 risk categories as given in Table I, the patients were cross-classified in 2*2 tables (risk factor category 1/category 2 vs. presence/absence of left atrial thrombi). The odds ratio of left atrial thrombi and corresponding 95% confidence interval were calculated for each of those risk factors. With respect to the variable spontaneous echo contrast, the patients were cross-classified in a 3*2 table (3 risk categories of spontaneous echo contrast versus presence/absence of left atrial thrombi). The odds ratio of left atrial thrombi and corresponding 95% confidence interval were calculated for risk category 2 versus risk category 1, and for risk category 3 versus risk

category 1. The analysis was performed using the SAS procedure FREQ[14].

Using a simple "moving average" method, a nonparametric regression of the risk of left atrial thrombi versus left atrial size was performed. The risk of left atrial thrombi for a given left atrial size S was calculated as the proportion of patients with left atrial thrombi of those patients who had a left atrial size in the interval $[S-W, S+W]$, where W is the size of the "window" of the moving average. A window size W of 0.4 mm was chosen (Figure 1, chapter 4).

Association between different risk factors:

During the multivariate analysis (see section 3.3.3 below) it transpired that certain risk factors for left atrial thrombi were strongly associated with each other, as well as being associated with the presence of left atrial thrombi. This could explain confounding effects that became obvious during the data analysis. For this reason it was instructive to investigate the relationships between certain risk factors for left atrial thrombi. Thus cross-tabulations of the patients with respect to the following pairs of risk factors were done: age versus rhythm, mitral regurgitation versus rhythm, spontaneous echo contrast versus left atrial size, spontaneous echo contrast versus rhythm, left ventricular ejection fraction versus left atrial size and left ventricular ejection fraction versus rhythm.

3.3.3 Multivariate analysis

In the multivariate analysis, the potential risk factors as listed in Table I were fitted in a multiple logistic regression model, with presence/absence of left atrial thrombi as the binary outcome. Stepwise selection was performed using the BMDP procedure LR[15]. The stepwise selection was started with the full model, that is, with all potential risk factors fitted. The p-values to-enter and to-remove were specified as 0.10 and 0.15, respectively. Odds ratios and corresponding 95% confidence intervals for the risk factors selected for the final model are reported.

Two different stepwise selection procedures were performed: in the first, all potential risk factors listed in Table I were fitted as the full model; in the second, all risk factors except spontaneous echo contrast were fitted. The second analysis was performed to determine a set of predictors for left atrial thrombi for the situation where transesophageal echocardiography is not available or cannot be performed, and consequently information on spontaneous echo contrast is not available. This is of importance in a third world environment with financial constraints where high technology apparatus, like a transesophageal probe for the detection of left atrial thrombi and in particular spontaneous echo contrast, is not always available.

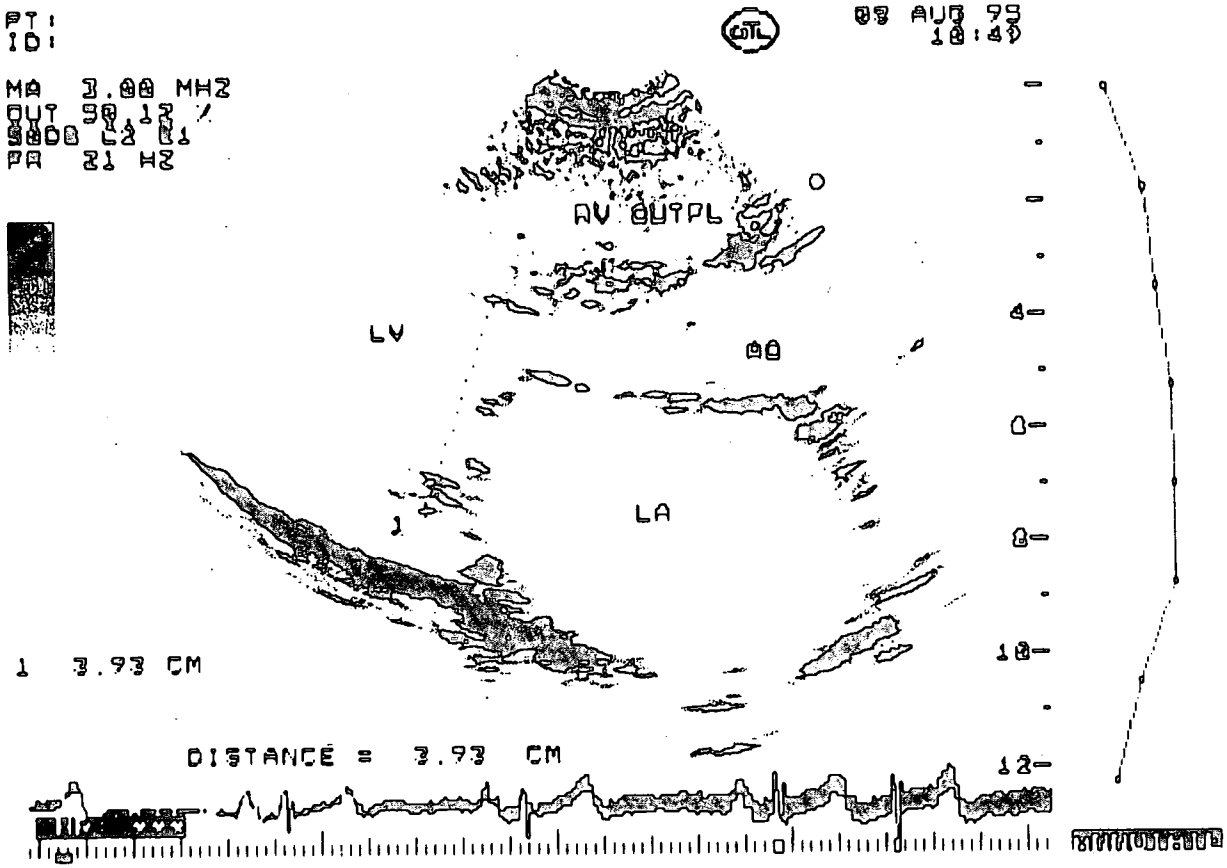

Fig. 1 End-diastolic and end-systolic dimensions for the calculations of left ventricular ejection fraction were aligned perpendicular to the major axis of the ventricular cavity at the level of the chordae tendinae

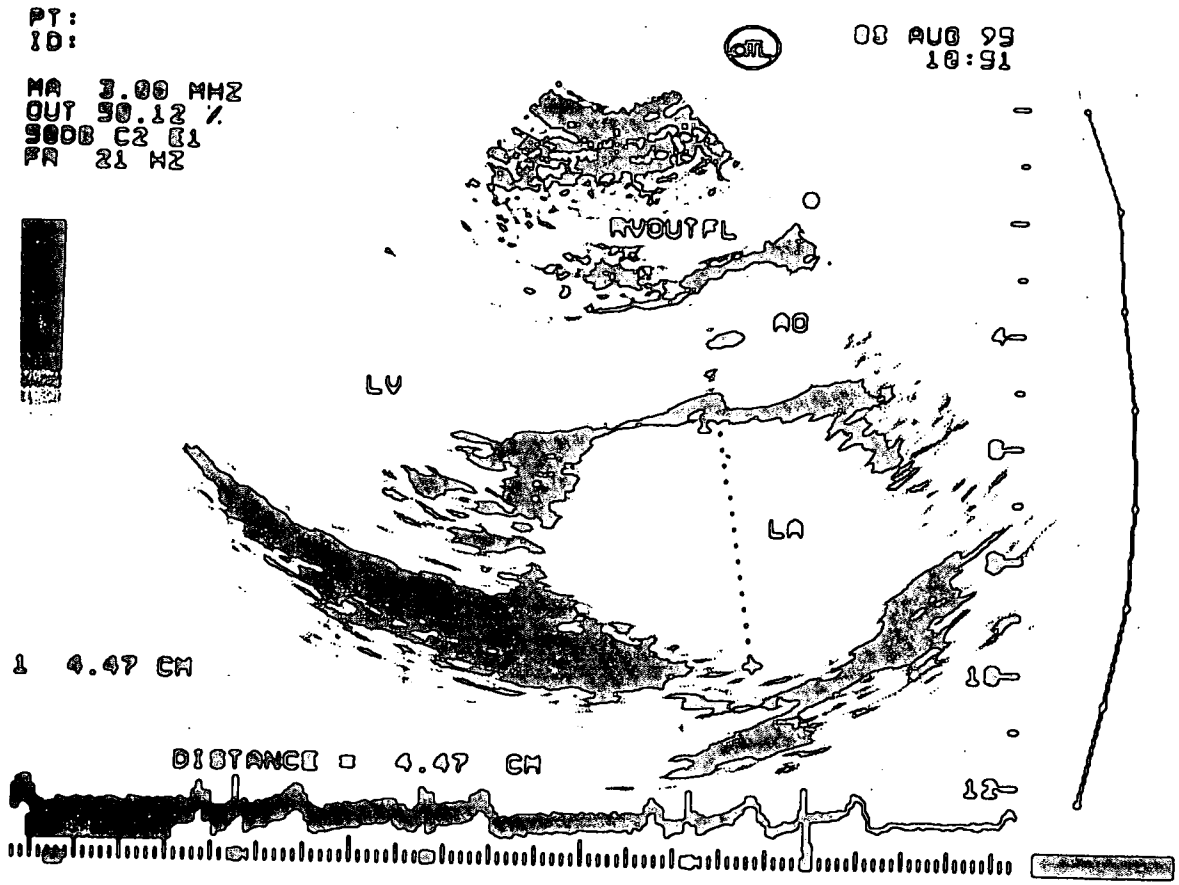

Fig. 2 The size of the left atrium was measured at the aortic valve plain perpendicular to the aortic root.

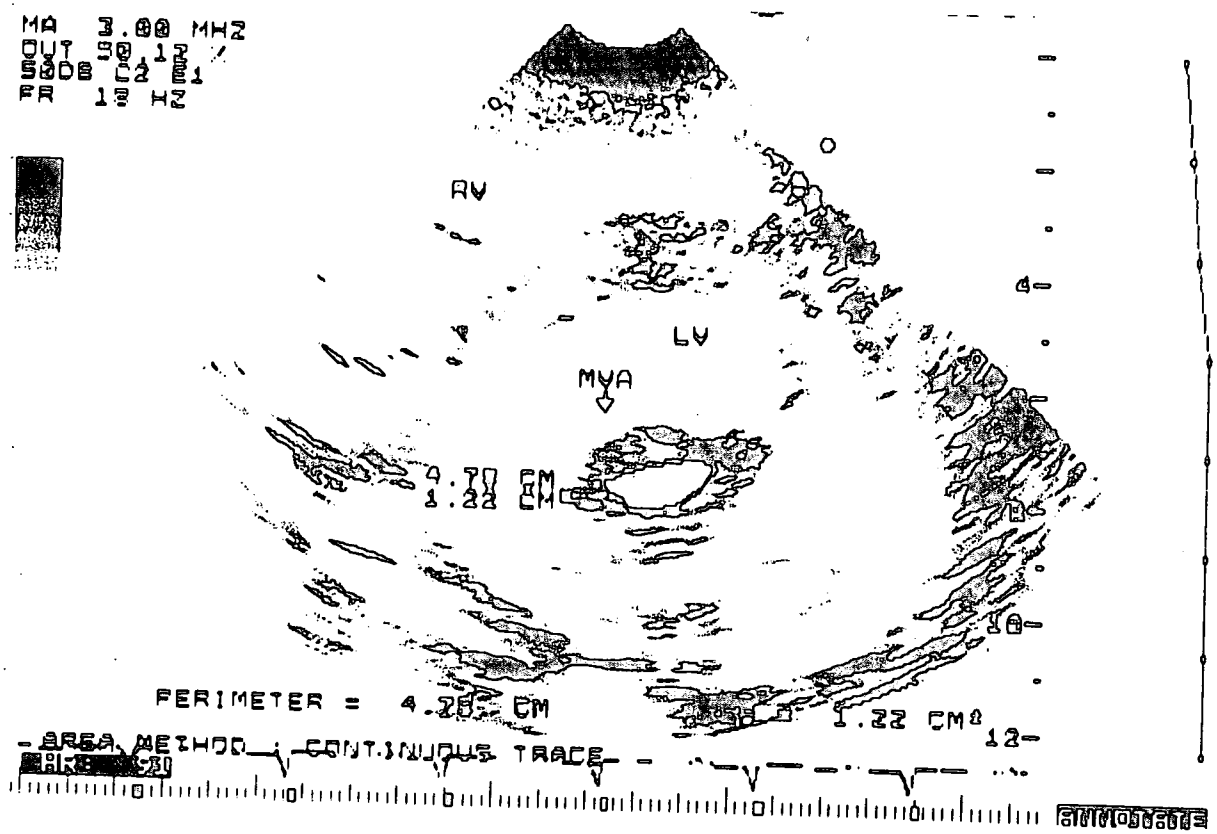

Fig. 3 The mitral orifice was imaged by two-dimensional echocardiography and planimetred to measure mitral valve area.

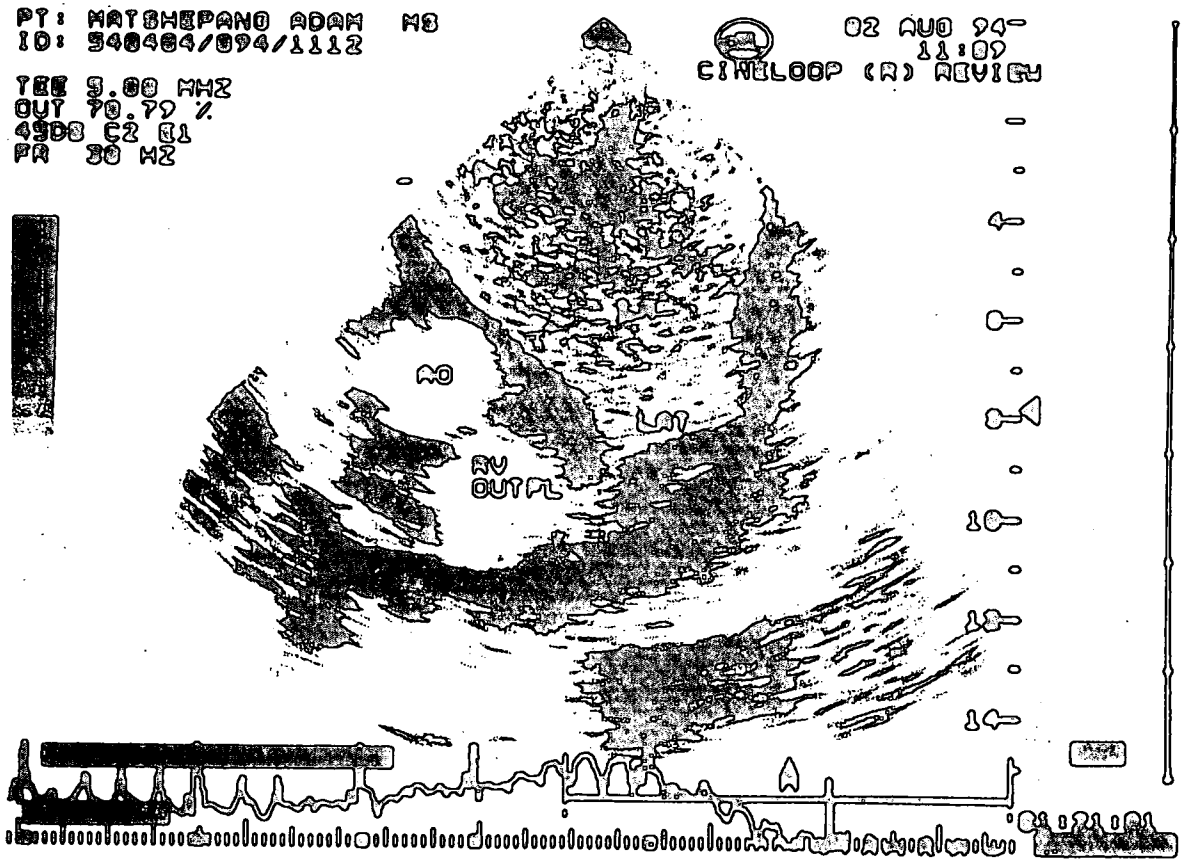

Fig. 4 The left atrial appendage was viewed from the basal short axis. Note the left atrial thrombus (LAT).

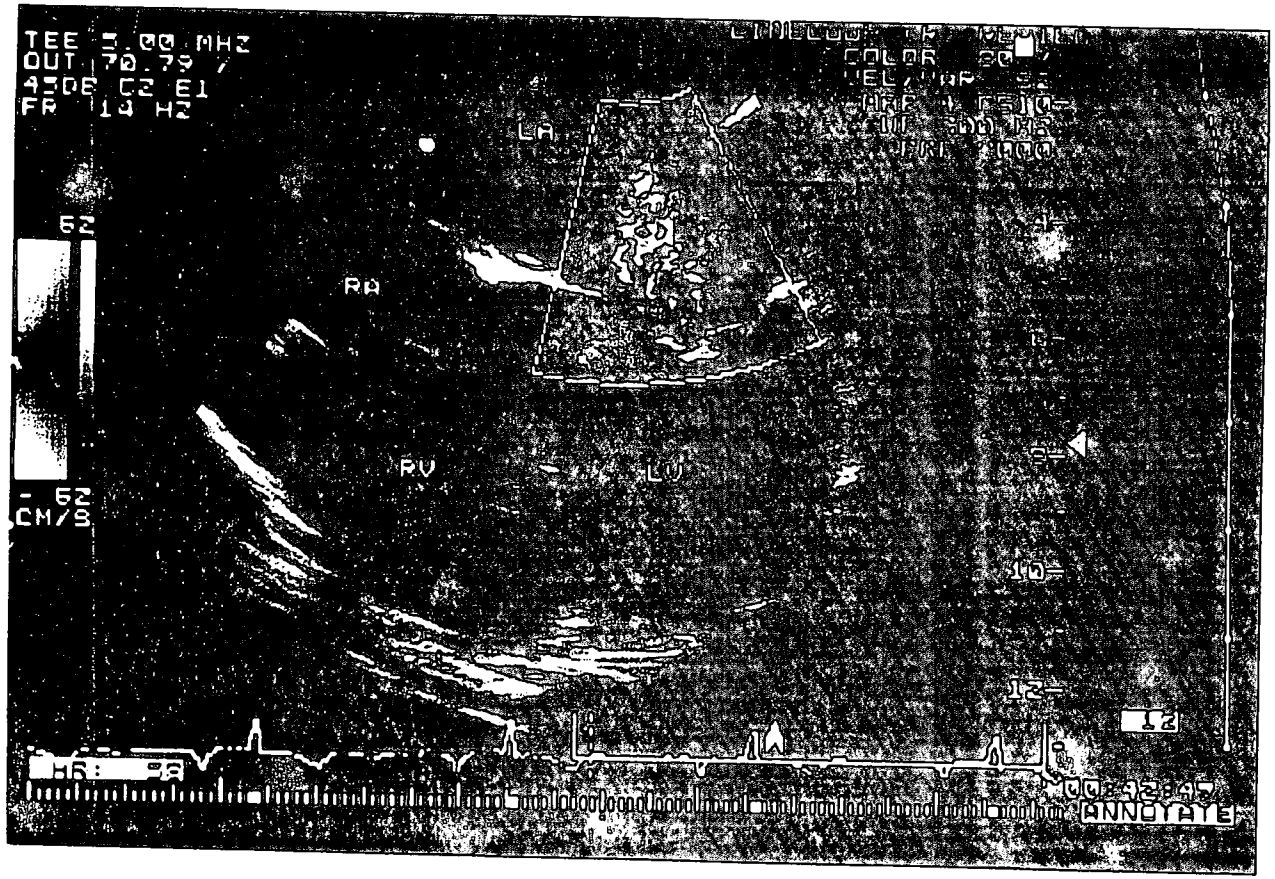

Fig. 5 Mitral regurgitation was graded in the 4 chamber view according to the area covered by the Doppler color flow jet.

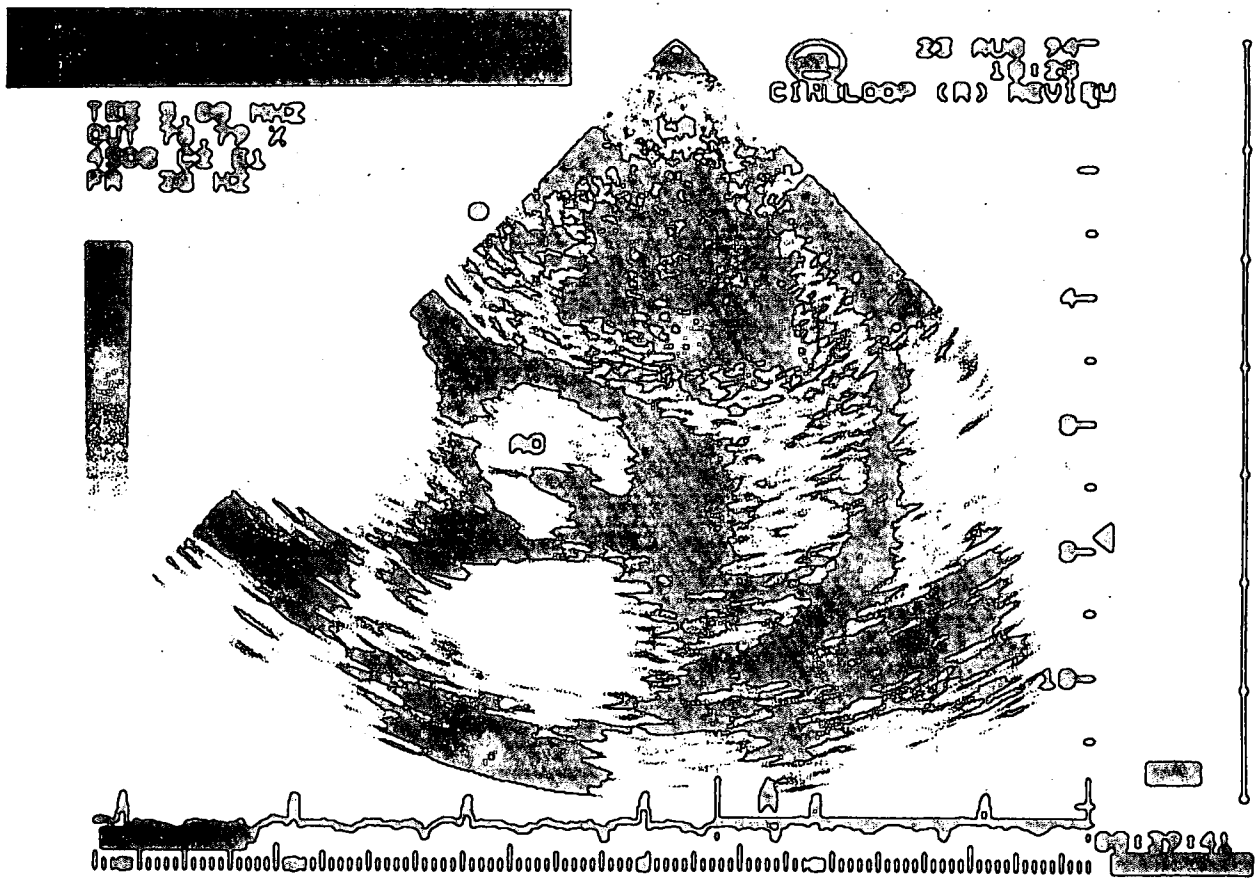

Fig. 6 Severe spontaneous echo contrast (SEC) can be visualized at the origin of the left atrial appendage.

Table I Potential risk factors for left atrial thrombi, and the risk categories investigated

Risk Factor	Original risk categories	Categories for univariate analysis	Code in logistic regression for multivariate analysis
Age (years)	≤40	≤40	0
	>40	>40	1
Sex	Female	Female	0
	Male	Male	1
Rhythm	Sinus rhythm	Sinus rhythm	0
	Atrial fibrillation	Atrial fibrillation	1
LA size (cm)	<4.8	<4.8	0
	≥4.8	≥4.8	1
MVA (cm^2)	<0.8	<0.8	0
	≥0.8	≥0.8	1
SEC	Absent	Absent	0
	Mild	Mild	1
	Moderate or severe	Moderate or severe	2
MR	Absent	Absent	0
	Mild	Mild to severe	1
	Moderate		
	Moderately severe		
	Severe		
LVEF (%)	≥50	≥50	0
	25 - 49	<50	1
	<25		

Abbreviations: LA - left atrial, MVA - mitral valve area, SEC - spontaneous echo contrast, MR - mitral regurgitation, LVEF - left ventricular ejection fraction.

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CHAPTER 4
RESULTS

4.1 General

Of the 146 patients, 92 (63%) had sinus rhythm and 54 (37%) atrial fibrillation (Table II). The age of the patients ranged between 16 and 67 years with a median of 34 years. Thirty-five patients (24%) had only mitral stenosis, while 111 patients (76%) had mitral stenosis and some form of mitral regurgitation. The mitral valve area ranged between 0.6 to 1.9 cm^2 with a median of 1.3 cm^2.

Left atrial thrombi were detected in 26 (17.8%) of patients. Of these 26 patients, 4 (15.4%) patients were in sinus rhythm and 22 (84.6%) in atrial fibrillation. Of the 120 patients without left atrial thrombi, 88 patients (73%) were in sinus rhythm and 32 patients (27%) were in atrial fibrillation (Table III). Left atrial thrombi extended from the left atrial appendage into the left atrium in 19 patients with left atrial thrombi, 5 patients had mural thrombi situated in the left atrium and 2 patients had left atrial thrombi situated in the left atrial appendage. Left atrial thrombi situated in the left atrial appendage were detected by transesophageal echocardiography alone in 16 (61.5%) patients. Left atrial mural thrombi were detected by transthorasic as well as transesophageal echocardiography in 10 (38.4%) patients. Nine (6%) of the patients presented with stroke (Table II). In 4 of these patients left atrial thrombus was diagnosed.

Seventy-two patients underwent open-heart mitral valve surgery. The presence of left atrial thrombi was confirmed in 12 of these patients by direct inspection. Five patients had left atrial thrombi situated in the left atrial appendage, 2 patients had left atrial thrombi located in the body of the left atrium and 5 patients had left atrial thrombi extending from the left atrial appendage into the left atrial posterior wall. With transesophageal echocardiography, compared to surgical findings, there was 1 false positive and 1 false negative diagnosis of left atrial thrombi. A sensitivity of 92%, a specificity of 98% and a positive predictive value of 92% and a negative predictive value of 98% were calculated for the detection of left atrial thrombi by transesophageal echocardiography (Table IV).

4.2 Univariate analysis

4.2.1 General

The results of the comparison of patients with left atrial thrombi and patients without left atrial thrombi with regard to the variables age, left atrial size and mitral valve area are given in Table V. The odds ratios and 95% confidence intervals associated with all potential risk factors, after categorization of the risk factors in risk categories, are given in Table VI.

4.2.2 Age

The median age of patients with left atrial thrombi was 33.5 years compared to 33.5 years in patients without left atrial thrombi (p=0.47, Mann-Whitney test) (Table V).

Of the 51 patients older than 40 years, 10 (20%) had left atrial thrombi and of the 95 patients 40 years and younger, 16 (17%) had left atrial thrombi (Table III). The odds ratio of left atrial thrombi in patients older than 40 years was 1.20 compared to patients 40 years and younger (95% confidence interval 0.50 to 2.89) (Table VI).

Considering the relationship between age and cardiac rhythm, it was found that of the 51 patients older than 40 years, 31 (61%) were in atrial fibrillation and 20 (39%) were in sinus rhythm. Of the 95 patients 40 years and younger, 23 (24%) were in atrial fibrillation and 72 (76%) were in sinus rhythm (Table VII). The odds ratio of atrial fibrillation in patients older than 40 years compared to younger patients was 4.85 (95% confidence interval 2.33 to 10.1).

4.2.3 Sex

Of the 117 female patients 20 (17%) had left atrial thrombi compared to 6 (21%) in the male patients (Table III). The odds ratio of left atrial thrombi in male patients compared to female patients was 1.27 (95% confidence interval 0.46 to 3.45).

4.2.4 Cardiac rhythm

Of the 92 patients in sinus rhythm, 4 (4%) had left atrial thrombi. Of the 54 patients with atrial fibrillation, 22 (41%) had left atrial thrombi (Table III). The odds ratio of left atrial thrombi in patients with atrial fibrillation compared to patients with sinus rhythm was 15.1 (95% confidence interval 4.83 to 47.3) (Table VI).

4.2.5 Left atrial size

The median left atrial size in patients with left atrial thrombi was 5.25 cm compared to 4.6 cm in patients without left atrial thrombi ($p<0.01$, Mann-Whitney test) (Table V). Of the 69 patients with left atrial size < 4.8 cm, 2 (3%) had left atrial thrombi. Of the 77 patients with left atrial size $\geq$ 4.8 cm, 24 (31%) patients had left atrial thrombi (Table III). The odds ratio of left atrial thrombi in patients with left atrial size $\geq$ 4.8 cm compared to patients with left atrial size < 4.8 cm was 15.2 (95 % confidence interval 3.42 to 66.7) (Table VI).

The risk of left atrial thrombi as a function of left atrial size is illustrated in Fig I. For a left atrial size of 4.5 cm or less, the risk of left atrial thrombi is relatively low (10% or less); for a left atrial size between 4.5 cm and 5.5 cm the risk increases with increasing left atrial size, until the risk reaches a plateau of about 40% for a left atrial size of 5.5 cm or higher.

4.2.6 Mitral valve area

The median mitral valve area in patients with left atrial thrombi was 1.2 cm^2 compared to 1.3 cm^2 in patients without left atrial thrombi (p=0.10, Mann-Whitney test) (Table V).

An odds ratio of left atrial thrombi in patients with a mitral valve area of $\geq$ 0.8 cm^2 compared to patients with a mitral valve area of less than 0.8 cm^2 was not calculated as there was only one patient with a mitral valve area of less than 0.8 cm^2 (Table III).

4.2.7 Spontaneous echo contrast

A mild or moderate/severe spontaneous echo contrast was detected in 111 patients of whom 25 (22.5%) had left atrial thrombi. Of the 35 patients without spontaneous echo contrast only 1 patient (2.9%) had a left atrial thrombus. Nine (11%) of the 84 patients with mild spontaneous echo contrast had left atrial thrombi, and 16 (59.3%) of the 27 patients with moderate or severe spontaneous echo contrast (Table III). This indicates a clear risk gradient from absent to mild to moderate/severe spontaneous echo contrast.

Considering the relationship of spontaneous echo contrast with left atrial size, it was found that of the 35 patients with no spontaneous echo contrast 8 (23%) had a left atrial size $\geq$ 4.8 cm, 45 (54%) of the 84 patients with mild spontaneous echo contrast had a left atrial size $\geq$ 4.8 cm, and 24 (89%) of the 27 patients with moderate or severe spontaneous echo contrast (Table VIII). Similarly, considering the relationship of spontaneous echo contrast with cardiac rhythm, it was found that of the 35

patients with no spontaneous echo contrast 5 (14%) were in atrial fibrillation, 32 (38%) of the 84 patients with mild spontaneous echo contrast were in atrial fibrillation, and 17 (63%) of the 27 patients with moderate or severe spontaneous echo contrast were in atrial fibrillation (Table VIII). Thus there is a clear risk gradient for both enlarged left atrial size and atrial fibrillation from absent to mild to moderate/severe spontaneous echo contrast.

4.2.8 Mitral regurgitation

26% of patients without mitral regurgitation had left atrial thrombi compared to 15% of patients with mild mitral regurgitation, 15% of patients with moderate mitral regurgitation, and 0% of patients with moderately severe mitral regurgitation (Table III).

As there was only one patient in the category moderately severe mitral regurgitation, no patient in the category severe mitral regurgitation, and the proportion of patients with left atrial thrombi in the categories mild mitral regurgitation and moderate mitral regurgitation was 15% in each case, it was decided to combine the last 4 categories and thus to categorize mitral regurgitation into only 2 categories, namely absent and mild to severe mitral regurgitation. Thus of the 111 patients where mild to severe mitral regurgitation was detected, 17 (15%) had left atrial thrombi and of the 35 patients without mitral regurgitation, 9 (26%) had left atrial thrombi. The odds ratio of left atrial thrombi in patients with mitral regurgitation compared to patients without mitral regurgitation is 0.52 (95% confidence interval 0.21 to 1.31) (Table VI).

Considering the relationship of mitral regurgitation with cardiac rhythm, it was found that of the 35 patients with no mitral regurgitation 8 (23%) were in atrial fibrillation compared to 46 (41%) of the 111 patients with mild to severe mitral regurgitation who were in atrial fibrillation (Table VII). The odds ratio of atrial fibrillation in patients with mitral regurgitation was 2.39 compared to patients with sinus rhythm (95% confidence interval 1.0 to 5.73).

4.2.9 Left ventricular ejection fraction

In 13 patients left ventricular ejection fraction could not be measured, and those patients were excluded from this analysis. Only 1 patient without left atrial thrombi had a left ventricular ejection fraction < 25%. Of the 37 patients with left ventricular ejection fraction 25-49%, 12 patients (32%) had left atrial thrombi, and of the 95 patients with left ventricular ejection fraction ≥ 50% 10 patients (11%) had left atrial thrombi (Table III).

Because there was only one patient in the category of left ventricular ejection fraction < 25% it was decided to combine the first two risk categories and thus to re-categorize left ventricular ejection fraction into 2 categories, namely left ventricular ejection fraction < 50% and ≥ 50%. Thus of the 38 patients with a left ventricular ejection fraction < 50%, 12 (32%) had left atrial thrombi, while of the 95 patients with a left ventricular ejection fraction ≥ 50%, only 10 (11%) had left atrial thrombi. The odds ratio of left atrial thrombi in patients with a left ventricular

ejection fraction less than 50% was 3.92 compared to patients with a left ventricular ejection fraction ≥ 50% (95% confidence interval 1.52 to 10.1).

Considering the relationship between left ventricular ejection fraction and cardiac rhythm, it was found that of the 38 patients with left ventricular ejection fraction < 50%, 23 (61%) were in atrial fibrillation, and 24 (25%) of the 95 patients with left ventricular ejection fraction ≥ 50% were in atrial fibrillation (Table IX). The odds ratio of atrial fibrillation in patients with left ventricular ejection fraction < 50% was 4.54 (95% confidence interval 2.04 to 10.1) compared to patients with left ventricular ejection fraction > 50%.

Similarly, considering the relationship between left ventricular ejection fraction and left atrial size, it was found that of the 38 patients with left ventricular ejection fraction < 50%, 26 (68%) had a left atrial size ≥ 4.8 cm, and 42 (44%) of the 95 patients with a left ventricular ejection fraction ≥ 50% had a left atrial size ≥ 4.8 cm (Table IX). The odds ratio of a left atrial size ≥ 4.8 cm in patients with a left ventricular ejection fraction < 50% was 2.73 (95% confidence interval 1.24 to 6.1) compared to patients with left ventricular ejection fraction ≥ 50%.

4.2.10 Summary: univariate analysis

In the univariate analysis, therefore, cardiac rhythm, left atrial size, spontaneous echo contrast, and left ventricular ejection fraction were identified as significant risk factors (Tables V and VI). Age, sex and mitral valve area did not seem to be significant risk factors.

Patients older than 40 years had a higher risk for atrial fibrillation than patients 40 years and younger. Patients with moderate or severe spontaneous echo contrast had a higher risk of atrial fibrillation or left atrial size ≥ 4.8 cm than did patients with absent or mild spontaneous echo contrast. The risk for atrial fibrillation was 2 times higher in patients with mitral regurgitation compared to patients without mitral regurgitation. Patients with left ventricular ejection fraction < 50% had a higher risk for atrial fibrillation or left atrial size ≥ 4.8 cm compared to those patients with left ventricular ejection fraction ≥ 50%.

4.3 Multivariate analysis

A multivariate analysis using stepwise logistic regression was done both with and without fitting spontaneous echo contrast as a potential predictor of left atrial thrombi (Tables Xa and Xb). In the model with spontaneous echo contrast the potential risk factors sex and mitral valve area were removed by stepwise logistic logistic regression. Thus, age, cardiac rhythm, left atrial size, mitral regurgitation, spontaneous echo contrast and left ventricular ejection fraction were selected for the final model as predictors for left atrial thrombi (Table Xa). The odds ratios and corresponding 95% confidence intervals associated with these predictors are given in Table XIa.

When spontaneous echo contrast was not fitted the same risk factors were selected for the final model as before. However, the odds ratio for left atrial thrombi associated with left atrial size was much higher

(approximately double) compared to the model with spontaneous echo contrast (Table XIb versus Table XIa). The odds ratios for age, atrial fibrillation and left ventricular ejection were similar for the two analyses, while the odds ratio for mitral regurgitation was less than half in the model without spontaneous echo contrast compared to the model with spontaneous echo contrast.

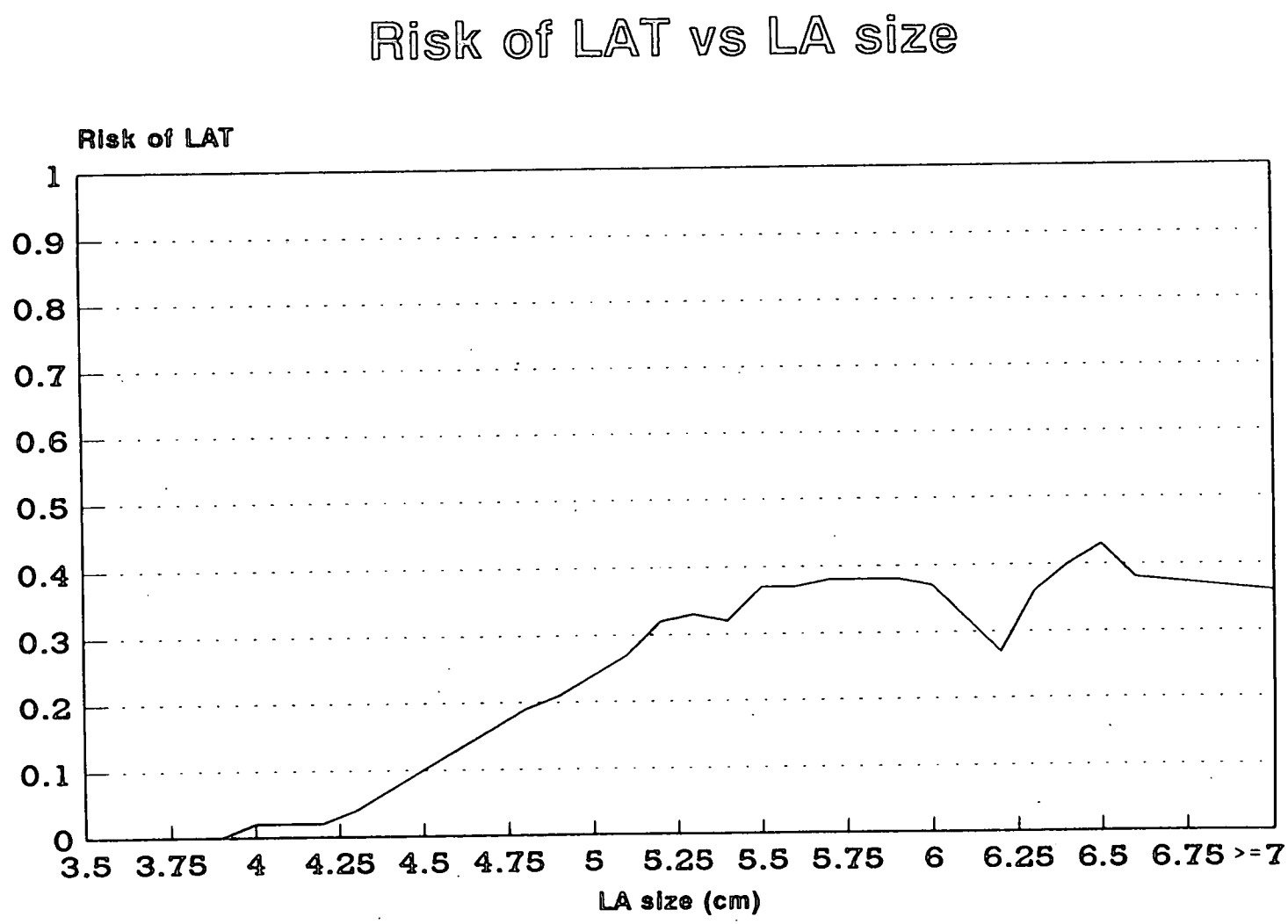

Fig. I A nonparametric regression of the risk of left atrial thrombi (LAT) versus left atrial (LA) size.

TABLE II Clinical characteristics of patients (n = 146)

Age (years)	Median	34
	Range	16-67
Sex	Female	117 (80%)
	Male	29 (20%)
Rhythm	Sinus rhythm	92 (63%)
	Atrial fibrillation	54 (37%)
Stroke		9 (6%)
Valve lesions	Mitral stenosis alone	35 (24%)
	Mitral stenosis/ Mitral regurgitation	111 (76%)
Mitral valve area (cm^2)	Median	1.3
	Range	0.6-1.9

TABLE III Association of potential risk factors with left atrial thrombi

Risk factor	Category	Patients without LAT (n = 120)	Patients with LAT (n = 26)	Total (n = 146)
Age	≤ 40 years	79 (83%)	16 (17%)	95
	> 40 years	41 (80%)	10 (20%)	51
Sex	Female	97 (83%)	20 (17%)	117
	Male	23 (79%)	6 (21%)	29
Rhythm	Sinus rhythm	88 (96%)	4 (4%)	92
	Atrial fibrillation	32 (59%)	22 (41%)	54
LA Size	< 4.8 cm	67 (97%)	2 (3%)	69
	≥ 4.8 cm	53 (69%)	24 (31%)	77
MVA	< 0.8 cm^2	1 (100%)	0 (0%)	1
	≥ 0.8 cm^2	129 (89%)	16 (11%)	145
SEC	Absent	34 (97%)	1 (3%)	35
	Mild	75 (89%)	9 (11%)	84
	Moderate or severe	11 (41%)	16 (59%)	27
MR	Absent	26 (74%)	9 (26%)	35
	Mild	82 (85%)	15 (15%)	97
	Moderate	11 (85%)	2 (15%)	13
	Moderately severe	1 (100%)	0 (0%)	1
	severe	0	0	0
LVEF*	<25%	85 (89%)	10 (11%)	95
	25-49%	25 (68%)	12 (32%)	37
	≥50%	1 (100%)	0 (0%)	1

Abbreviations: LA size - left atrial size, MVA - mitral valve area, SEC - spontaneous echo contrast, MR - mitral regurgitation; LVEF - left ventricular ejection fraction.

*Total: n = 133 (see section 4.2.9)

Table IV Sensitivity and specificity of transesophageal echocardiography in the detection of left atrial thrombi (LAT) (n = 72)

Transesophageal echocardiography	Surgical inspection		Total (n = 72)
	Patients with LAT (n = 12)	Patients without LAT (n = 60)	
Patients with LAT	11	1	12
Patients without LAT	1	59	60

Sensitivity: (True positive) / (true positive + false negative) = 92%

Specificity: (True negative) / (true negative + false positive) = 98%

Positive predictive value: (True positive) / (true positive + false positive) = 92%

Negative predictive value: (True negative) / (true negative + false negative) = 98%

TABLE V **Univariate analysis: comparison of patients with and without left atrial thrombi with respect to Age, LA size and MVA.**

	Patients without LAT (n=120)		Patients with LAT (n=26)		p-value*
	Median	Range	Median	Range	
Age (years)	33.5	16-67	33.5	16-64	0.47
LA size (cm)	4.6	2.8-7.4	5.25	4.4-8.0	0.01
MVA (cm^2)	1.3	0.6-1.9	1.2	0.8-1.7	0.10

*Mann-Whitney test comparing patients with and without LAT.

Abbreviations: LAT - left atrial thrombi, LA - left atrial, MVA - mitral valve area.

TABLE VI Univariate analysis: odds ratios and confidence intervals associated with potential risk factors for left atrial thrombi

Risk factor	Odds ratio *	95% Confidence interval
Age	1.20	0.50 ; 2.89
Sex	1.27	0.46 ; 3.45
Rhythm	15.1	4.83 ; 47.3
LA size	15.2	3.42 ; 66.7
SEC (2)	4.08	0.50 ; 33.3
SEC (3)	49.5	5.88 ; 500
MR	0.52	0.21 ; 1.31
LVEF	3.92	1.52 ; 10.1

*Odds for risk factor category 2 over odds for risk factor category 1, for all risk factors except SEC ; for SEC, odds for risk category 2 over odds for risk category 1 [SEC (2)] and odds for risk category 3 over odds for risk category 1 [SEC (3)]. Risk factor categories as defined in Table I.

Abbreviations: LA - left atrial, SEC (2) - mild spontaneous echo contrast, SEC (3) - moderate or severe spontaneous echo contrast, MR - mitral regurgitation, LVEF - left ventricular ejection fraction.

Table VII Association of age and mitral regurgitation with cardiac rhythm.

		Cardiac rhythm		Total
		Sinus rhythm	AF	(n=146)
Age	≤ 40 years	72 (76%)	23 (24%)	95
	> 40 years	20 (39%)	31 (61%)	51
MR	Absent	27 (77%)	8 (23%)	35
	Mild to severe	65 (59%)	46 (41%)	111

Abbreviations: AF - atrial fibrillation, MR - mitral regurgitation

Table VIII Association of spontaneous echo contrast with left atrial size and cardiac rhythm.

	LA size		Cardiac Rhythm		
SEC	<4.8 cm	≥4.8 cm	Sinus rhythm	AF	Total (n=146)
Absent	27 (77%)	8 (23%)	30 (86%)	5 (14%)	35
Mild	39 (46%)	45 (54%)	52 (62%)	32 (38%)	84
Moderate or severe	3 (11%)	24 (89%)	10 (37%)	17(63%)	27

Abbreviations: AF - atrial fibrillation, LA - left atrial, SEC - spontaneous echo contrast

Table IX Association of left ventricular ejection fraction with left atrial size and cardiac rhythm.

	LA size		Cardiac rhythm		Total (n = 133)
LVEF	<4.8 cm	≥4.8 cm	Sinus rhythm	AF	
≥50%	53 (56%)	42 (44%)	71 (75%)	24 (25%)	95
<50%	12 (32%)	26 (68%)	15 (39%)	23 (61%)	38

Abbreviations: AF - atrial fibrillation, LA - left atrial, LVEF - left ventricular ejection fraction.

Table Xa Multivariate analysis: F-statistics and p-values associated with potential risk factors (final model selected by stepwise logistic regression; full model including SEC)

Risk factors	Approximate F-to-enter*	Approximate F-to-remove*	p-value
Age		2.91	0.0907
Sex	0.65		0.4199
Rhythm		12.58	0.0005
LA size		3.52	0.0629
SEC		5.56	0.0049
MVA	0.02		0.8818
MR		2.81	0.0960
LVEF		3.86	0.0516

*Degrees of freedom 1;125 for all factors except SEC; for SEC the degrees of freedom are 2;125

Abbreviations: LA - left atrial, SEC - spotaneous echo contrast, MVA - mitral valve area, MR - mitral regurgitation, LVEF - left ventricular ejection fraction.

Table Xb Multivariate analysis: F-statistics and p-values associated with potential risk factors (final model selected by stepwise logistic regression; full model excluding SEC)

Risk factors	Approximate F-to-enter*	Approximate F-to-remove*	p-value
Age		2.90	0.0913
Sex	1.41		0.2370
Rhythm		13.81	0.0003
LA size		7.09	0.0087
MVA	0.99		0.3228
MR		8.46	0.0043
LVEF		2.19	0.1414

*Degrees of freedom 1;127

Abbreviations: LA - left atrial, SEC - spotaneous echo contrast, MVA - mitral valve area, MR - mitral regurgitation, LVEF - left ventricular ejection fraction.

TABLE XIa Multivariate analysis: odds ratios and confidence intervals associated with potential risk factors included in the final model selected by stepwise logistic regression (full model including SEC)

Risk factor	Odds ratio *	95% Confidence interval
Age	0.32	0.07 ; 1.45
AF	17.5	2.08 ; 109
LA size	4.09	0.75 ; 22.5
MR	0.25	0.04 ; 1.63
SEC (2)	2.19	0.20 ; 24.1
SEC (3)	18.1	1.34 ; 243
LVEF	3.34	0.83 ; 13.4

*Odds for risk factor category 2 over odds for risk factor category 1, for all risk factors except SEC; for SEC, odds for risk category 2 over odds for risk category 1 [SEC (2)] and odds for risk category 3 over odds for risk category 1 [SEC (3)]. Risk factor categories as defined in Table I.

Abbreviations: AF - atrial fibrillation, LA - left atrial, MR - mitral regurgitation, SEC (2) - mild spontaneous echo contrast, SEC (3) - moderate or severe spontaneous echo contrast, LVEF - left ventricular ejection fraction.

TABLE XIb Multivariate analysis: odds ratios and confidence intervals associated with potential risk factors included in the final model selected by stepwise logistic regression (full model excluding SEC)

Risk factor	Odds ratio *	95% Confidence interval
Age	0.33	0.08 ; 1.25
AF	22.6	4.08 ; 125
LA size	8.48	1.65 ; 43.6
MR	0.10	0.02 ; 0.51
LVEF	2.43	0.71 ; 8.26

*Odds for fisk factor category 2 over odds for risk factor category 1 ; risk factor categories as defined in Table 1.

Abbreviations: AF - atrial fibrillation, LA - left atrial, MR - mitral regurgitation, LVEF - left ventricular ejection fraction, SEC - spontaneous echo contrast.

CHAPTER 5
DISCUSSION

5.1 General

Both the univariate and multivariate analyses identified atrial firillation, left atrial size ≥ 4.8 cm, moderate or severe spontaneous echo contrast and left ventricular ejection fraction < 50% as risk factors for left atrial thrombi. Both analyses identified mild to severe mitral regurgitation as a protective factor for left atrial thrombi. Both analyses indicated that sex and mitral valve area are not significant risk factors.

In the univariate analysis, age more than 40 years was not found to be a significant risk factor, while, unexpectedly, the multivariate analysis appeared to indicate age older than 40 years as a protective factor for left atrial thrombi. In the following, these results are discussed in detail.

5.2 Cardiac rhythm

Left atrial thrombi were detected in 4% of patients with mitral stenosis with sinus rhythm compared to 41% of patients with mitral stenosis and atrial fibrillation. There is no doubt about the role of atrial fibrillation as a risk factor for left atrial thrombi in patients with mitral stenosis. Coulshed et al found atrial fibrillation, with thrombus formation in the atrium, as the main cause of predisposition to systemic embolism[1].

Our data confirm that atrial fibrillation is a significant predictor of left atrial thrombi as found by both the univariate and multivariate analysis. However, 63% of all the patients and 15% of patients with left atrial thrombi were in sinus rhythm. These numbers speak against the conventional wisdom that left atrial stasis and thrombus formation are exclusively the domain of atrial fibrillation. These are the patients that should be protected against left atrial thrombi and systemic embolism as they do not, at present, qualify for routine anticoagulant therapy.

5.3 Age

Higher age alone was not found to be a risk factor for left atrial thrombi in patients with mitral stenosis. This was confirmed by both the univariate and the multivariate analysis. In fact, age above 40 years appeared to be protective of left atrial thrombi in the multivariate analysis (odds ratio smaller than 1). It is, however, important to note that patients over 40 years had an increased prevalence of atrial fibrillation. Of the 51 patients older than 40 years, 31 (60.8%) were in atrial fibrillation and 20 (39.2%) in sinus rhythm. Of the 95 patients who were 40 years and younger, 23 (24.2%) were in atrial fibrillation and 72 (75.8%) in sinus rhythm. The odds ratio of atrial fibrillation in patients older than 40 years was 4.85 compared to patients younger than 40 years (95% confidence interval 2.33 to 10.09). This confounding effect by atrial fibrillation is probably the reason why previous studies, using only univariate analysis, found age over 40 years to be a risk factor for left atrial thrombi.

A possible reason why age appears to be protective of left atrial thrombi in patients with mitral stenosis in the multivariate analysis is that atrial fibrillation complicated by systemic thromboembolism either prevents them from reaching old age or leads to earlier surgical intervention. Thus the presumed causal relationship between higher age and the presence of left atrial thrombi may be reversed: age does not cause or protect from left atrial thrombi, but left atrial thrombi prevent patients from reaching a high age.

5.4 Sex

Sex was not found to be a significant risk factor for left atrial thrombi. Although there were more female patients with mitral stenosis than males, the prevalence of left atrial thrombi was similar in males and females. This finding was confirmed in the multivariate analysis.

5.5 Left atrial size

Left atrial enlargement $\geq$ 4.8 cm was found to be a significant risk factor for left atrial thrombi both in the univariate and multivariate analysis. Although a left atrial size greater than 4 cm is positively correlated to the development of atrial fibrillation[2], it is not known at what stage large left atrium enlargement appears to be a risk for left atrial thrombi in patients with mitral stenosis with sinus rhythm. Data on the first 69 patients indicated that left atrial enlargement $\geq$ 4.8 cm appeared to predict the presence of left atrial thrombi, but this hypothesis had to be investigated further because the cut-off of $\geq$ 4.8 cm was selected from the data. In the

follow-up study on 77 patients left atrial size ≥ 4.8 cm was confirmed to be an independent risk factor for left atrial thrombi when taking atrial fibrillation and mitral regurgitation into account. This is an important new finding as it leads to early identifiction of patients with mitral stenosis with sinus rhythm at high risk for left atrial thrombi.

5.6 Mitral regurgitation

The presence of mitral regurgitation decreased the risk for left atrial thrombi, as indicated by the univariate analysis. This was confirmed by the multivariate analysis and supports the finding of Beppu[3] and others[4] that the incidence of left atrial thrombi is inversely related to the degree of mitral regurgitation.

5.7 Spontaneous echo contrast

In a previous study spontaneous echo contrast indicated an increased thromboembolic risk in patients with mitral stenosis. Patients with spontaneous echo contrast had a significantly larger left atrial diameter, were mostly in atrial fibrillation and had a greater incidence of both left atrial thrombi and a history of arterial embolic episodes than did patients without spontaneous echo contrast[5]. In our study both the univariate and multivariate analysis indicated spontaneous echo contrast to be a risk factor for left atrial thrombi. Odds ratios for mild versus absent and moderate or severe versus absent spontaneous echo contrast demonstrated a clear risk gradient for left atrial thrombi from absent to mild to moderate or severe spontaneous echo contrast. Our data therefore

confirm moderate or severe spontaneous echo contrast as a risk factor for left atrial thrombi.

The odds ratio of atrial fibrillation in patients with spontaneous echo contrast was 4.74 compared to patients without spontaneous echo contrast (95% confidence interval 1.71 to 13.13). The odds ratio of the presence of a left atrial size size $\geq$ 4.8 cm in patients with spontaneous echo contrast was 5.55 compared to patients without spontaneous echo contrast (95% confidence interval 2.31 to 13.13). Thus there is a strong association of spontaneous echo contrast with atrial fibrillation and left atrial enlargement. This is in agreement with previous studies which found left atrial stasis, as indicated by left atrial spontaneous echo contrast, to be reasonably predicted by the presence of atrial fibrillation and by the degree of left atrial dilatation[6,7]

The association between spontaneous echo contrast and left atrial size also explains the difference in the estimated odds ratio for left atrial size in the two multivariate analyses, namely one analysis including spontaneous echo contrast and the other excluding spontaneous echo contrast. When spontaneous echo contrast is fitted in the model, the odds ratio for left atrial size is only about half compared to the case when spontaneous echo contrast is not fitted (Tables XIa and XIb). Thus spontaneous echo contrast in part stands in for the risk factor left atrial size. However, our multivariate analysis shows that both left atrial size and spontaneous echo contrast are included in the final model which indicates that left atrial size and spontaneous echo contrast are to a certain degree independent risk factors for left atrial thrombi.

5.8 Left ventricular ejection fraction

Impaired left ventricular systolic function occurred in 28.6% of patients with mitral mitral stenosis. Our data are similar to the finding of Snyder II et al , in that 29% of their patients had a left ventricular ejection fraction < 50%[8]. The risk for left atrial thrombi was four times higher in patients with impaired left ventricular function compared to those with normal left ventricular function in the univariate analysis, and this was confirmed in the multivariate analysis.

Patients with left ventricular ejection fraction < 50% had a higher risk of atrial fibrillation (odds ratio 4.54; 95% confidence interval 2.04 to 10.08) and left atrial enlargement (odds ratio 2.73; 95% confidence interval 1.24 to 6.05) compared to patients with a left ventricular ejection fraction ≥ 50%. These factors could explain the higher risk for left atrial thrombi in patients with impaired left ventricular function.

In 13 patients the left ventricular ejection fraction could not be measured due to abnormal septal movement. Septal movements reflects relative filling of the two ventricles[9,10]. In mitral stenosis an exaggerated posterior movement of the interventricular septum or diastolic dip results from unequal filling of the two ventricles and distortion of the right ventricle[11]. The explanation of the distortion is that mitral stenosis restricts the filling of the left ventricle in early diastole, whereas the unobstructed tricuspid valve permits rapid filling of that ventricle. In early diastole the right ventricle fills more rapidly and the septum bulges

toward the left ventricle. This abnormal septal movement is further influenced by chronic pressure overload of the right ventricle and consequently distortion of the interventricular septum during ventricular systole[12,13,14,15]. Hypertrophy of the right ventricle and interventricular septum lead to the distortion of the normal circular ventricular cavity. This distortion usually produces a flattening of the interventricular septum during ventricular systole. Right ventricular volume overload produces dilatation of the right ventricle[16,17,18]. The other finding finding with right ventricular volume overload is a peculiar motion of the interventricular septum[19,20,21]. The abnormality seen on M-mode is rapid anterior movement of the interventricular septum with the onset of ventricular systole. The increased diastolic filling of the right ventricle produces an indentation of the septum toward the left ventricle[22]. With ventricle systole this indentation is rapidly corrected and the septum moves toward the right ventricle. This paradoxical movement of the interventricular septum may thus influence the measurement of left ventricular function.

Gash et al concluded that the low left ventricular ejection performance indexes found in many patients with mitral stenosis are frequently due to altered loading conditions. The high afterload is caused by reduced end-systolic left ventricular wall thickness and, occasionally, by high systemic vascular resistance. Because left ventricular filling is impaired by the stenotic mitral valve, this elevation in afterload is not offset by the Frank-Starling mechanism. Therefore, low ejection performance indexes underestimate left ventricular systole muscle function in most of such patients[23].

5.9 Mitral valve area

The severity of the mitral stenosis alone, as measured by the mitral valve area, did not appear to be a risk factor for left atrial thrombi. This negative finding could be because the study population was too small or that not enough patients with severe mitral stenosis were included. It may also be seen in a positive light in that patients with mitral stenosis either present themselves earlier due to symptoms or that there is an increased sensitivity towards the diagnosis of mitral stenosis, especially with diagnostic tools like transthoracic and transesophageal echocardiography.

It is of interest that the patient with mitral valve area less than 0.8 cm^2 was in the group of patients without left atrial thrombi. No difference in mitral valve area was found when those with and without left atrial thrombi were compared. However, in the patients with left atrial thrombi, the left atrial size was significantly greater than those without left atrial thrombi ($p<0.01$, Mann Whitney test). Enlargement of the left atrium greater than 4.0 cm is positively correlated to the development of atrial fibrillation which contributes to the high risk of thromboembolism. Therefore, obstruction at the mitral valve remains established as of prime importance in the pathogenesis of left atrial thrombi and embolism.

In summary, atrial fibrillation, left atrial enlargement ≥ 4.8 cm, left ventricular ejection fraction < 50% and moderate or severe spontaneous echo contrast emerged as the most important risk factors for left atrial thrombi in patients with mitral stenosis, both in the univariate and in the multivariate analysis.

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CHAPTER 6
CONCLUSION

At present, long-term anticoagulation with warfarin is indicated only either in patients with rheumatic mitral valve disease (either stenosis or regurgitation) of any severity in the presence of atrial fibrillation, or in patients with previous systemic emboli without regard to the severity of the valvular disease or the presence of rhythm disturbance. Anticoagulant therapy is not routinely instituted in patients with left atrial enlargement[1,2]. Because the risk of atrial fibrillation is high for patients with rheumatic mitral disease and a very large atrium, left atrial diameter greater than 55 mm, it has been suggested that such patients, even when in normal sinus rhythm should receive anticoagulant therapy[3].

However, we have shown that left atrial size $\geq$ 4.8 cm is an independent risk factor for left atrial thrombi. For the first time a cutoff for left atrial enlargement in patients with mitral stenosis but in sinus rhythm has been identified that indicates the high risk patient for left atrial thrombi and systemic embolism.

Impaired left ventricular ejection fraction < 50% has been found to be a high risk for left atrial thrombi. This confirms the finding of Roberts that thrombus in the left atrial appendage is common in any low cardiac output state as well as stenotic lesions of the mitral valve[4].

We have confirmed atrial fibrillation to be the single most important risk factor for left atrial thrombi. Any patient with mitral valve stenosis with atrial fibrillation should reveive anticoagulant therapy. Patients with mitral stenosis with sinus rhythm should be placed routinely on anticoagulant therapy if they have a left atrial size $\geq$ 4.8 cm, impaired left ventricular function < 50% or moderate to severe spontaneous echo contrast in the left atrium.

Furthermore, the decision whether to put a patient with mitral stenosis on anticoagulant therapy can be made in any clinical practice. A good clinical examination will identify the patient with atrial fibrillation, and both left atrial size and left ventricular ejection fraction can be measured by transthoracic two-dimensional echocardiography. Although spontaneous echo contrast cannot always be determined accurately by transthoracic echocardiography, left atrial enlargement and atrial fibrillation predict its presence.

Finally, since the presence of left atrial thrombi can be reliably demonstrated only by transesopheal echocardiography, the more aggressive therapy that these patients deserve can be documented only with this form of testing. Transesophageal echocardiography provides important information concerning the location of left atrial thrombus for anticipated mitral balloon valvuloplasty and the morphology of the valve structure; it provides also a highly accurate assessment of the degree of mitral insufficiency, greatly influencing the therapeutic options of valve repair or replacement. It would

seem that the vast majority of patients with mitral stenosis should undergo this examination during the course of their disease.

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SUMMARY

Left atrial thrombus with systemic emboli is a serious complication and economic burden in patients with mitral stenosis. At present long-term anticoagulation with warfarin is indicated in patients with rheumatic mitral valve disease only in the presence of atrial fibrillation or with previous systemic emboli.

In an exploratory study we found the severity of the mitral valve lesion alone not to be a risk factor for left atrial thrombi in mitral stenosis, but when complicated by atrial fibrillation or left atrial enlargement, especially $\geq$ 4.8 cm, there appears to be a higher risk for the development of left atrial thrombi.

The purpose of this study was to investigate the risk factors for left atrial thrombi in patients with mitral stenosis and to identify criteria for anticoagulant therapy to prevent thromboembolism.

One hundred and forty six patients with predominant mitral stenosis (mitral valve area less than 2.0 cm^2) and on no anticoagulant therapy were examined by transthoracic and transesophageal echocardiography for the detection of left atrial thrombi. Age, sex, rhythm, left atrial size, mitral valve area, spontaneous echo contrast, mitral regurgitation and left ventricular ejection fraction were investigated as possible risk

factors for left atrial thrombi. Both a univariate and multivariate analysis of the data were performed.

Left atrial thrombi were detected in 26 (17.8%) of the 146 patients. Through multivariate analysis, atrial fibrillation, left atrial size $\geq$ 4.8 cm, left ventricular ejection fraction <50% and moderate or severe spontaneous echo contrast have been found to be independent risk factors for left atrial thrombi, and should be included as indications for anticoagulant therapy to prevent thromboembolism.