**MD Thesis**

# Cardiac ultrasound for the evaluation of patients undergoing balloon mitral valvotomy for rheumatic mitral stenosis.

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## Acknowledgements

I will not forget the nights spent with Dr Shaw in a dimly lit room amongst mountains of paper. I am grateful for his teaching, ideas, guidance and encouragement. Dr Northridge developed my initial interest in echocardiography. Under his excellent tuition I gained the skills required to accomplish this work and the echo training I received continues to be invaluable during my career in cardiology. I was fortunate to gain a BHF Fellowship and I am grateful for the expert advice from the University department of Medical Physics (Professor McDicken, Dr Pye), Dr Masani and Professor Fox.

I thank Vicky, Merryn and Hamish for their patience and support.

## ABSTRACT

Since its introduction by Inoue in 1984, percutaneous balloon mitral valvotomy (BMV) has been widely used as an alternative to surgery for the treatment of rheumatic mitral stenosis. The success of BMV relies heavily on the presence of valve morphology suitable for balloon dilatation and cardiac ultrasound has become the cornerstone for assessment of patients undergoing this procedure. In young patients with pliant valves and predominant commissural fusion, the success of BMV has been well documented and for such patients this is the treatment of choice. However, with the disappearance of rheumatic fever in developed countries, patients presenting with mitral stenosis to centres such as ours are typically elderly. They often have valve anatomy less suitable for balloon dilatation but surgical risk is also much higher. Experience of BMV in this population is limited, results are less predictable and the selection of patients less straightforward.

In a centre with the largest experience of BMV in the UK, I have reported on a series of 405 consecutive patients, mean age 60.7 years, 27.7% over 70 years old. Longer term outcome was recorded in 300 patients over 10 years. I studied the anatomical and clinical characteristics of this diverse group of patients. I evaluated the role of BMV as a definitive treatment where echocardiography showed valve anatomy to be suitable for balloon dilatation and as a palliative option in older patients with severe degenerative valve disease but high surgical risk. I identified factors predicting immediate haemodynamic and longer term functional success. I studied in detail the strengths and limitations of two-dimensional transthoracic, transoesophageal and three-dimensional echocardiography for the assessment of patients undergoing BMV. Importantly, I have been able to show that specific evaluation of mitral commissural morphology, a feature not included in current echocardiographic scoring systems, was a powerful predictor of outcome and could improve the selection of patients referred for BMV in this older population.

## Declaration

I declare that this thesis is my own work and has not been submitted for any other degree or professional qualification.

Signed

Dr Nilesh Sutaria MBChB, MRCP

## List of Tables and figures in order of appearance in text

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## List of abbreviations

| | |
|---|---|
| AF | Atrial fibrillation |
| ANOVA | Analysis of variance |
| BMV | Balloon mitral valvotomy |
| CAD | Coronary artery disease |
| COP | Cardiac output |
| ES | Echo Score |
| LA | Left atrium |
| MR | Mitral regurgitation |
| MVA | Mitral valve area |
| MVR | Mitral valve replacement |
| NYHA | New York Heart Association class |

# CHAPTER ONE:
# Introduction

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## 1.1 Rheumatic fever: epidemiology and influence on demographics of valvular heart disease

Mitral stenosis is almost always the result of a previous attack of rheumatic fever, although in 50% of cases this is subclinical. In many under-developed countries, the incidence of acute rheumatic fever has increased over the last 50-60 years and exceeds 100 per 100,000 [World Health Organisation 1988]. Difficulty in accessing health care rapidly leads to inadequate treatment of streptococcal sore throat and secondary prophylaxis is rarely implemented. Moreover, overcrowding and poor living conditions have accelerated the propagation of the disease. In these areas rheumatic fever adopts a malignant form and advances rapidly. Recurrent untreated streptococcal infection and subsequent recurrent rheumatic carditis results in severe mitral stenosis in young patients and is the commonest cause of acquired heart disease in school age children and young adults world-wide. Hospital statistics from most developing nations reveal that approximately 10-35% of all cardiac admissions are for patients with rheumatic fever or chronic rheumatic heart disease [Narula et al 1999]. Accordingly, valve replacement accounts for the majority of cardiac surgery in these countries.

In contrast, the incidence of rheumatic fever in the United States and Western Europe has fallen dramatically over the last century. In the early 1900s during the industrial revolution, rheumatic fever was still one of the leading causes of morbidity and mortality perhaps due to overcrowding in urban areas. The annual incidence in the US at this time was 100-200 cases per 100,000. By the late 1940s the incidence had reduced to 50 per 100,000 and the rate fell further to 0.5 per 100,000 by the early 1980s [Gordis et al 1985]. In England and Wales there were 81 deaths notified as resulting from rheumatic fever in 1944, 64 in 1954, 7 in 1964 and 4 in 1975 [Hutchison 1989]. This decline has been attributed to the use of prophylactic penicillin and socio-economic advances. There was no actual decrease in the incidence of streptococcal pharyngitis per se; instead there was a disappearance of rheumatogenic strains in the more affluent communities of developed countries [Stollerman G et al 1997]. During 1985-1988, the medical community in the US were surprised by four unexpected outbreaks of rheumatic

fever which represented a 20-fold increase in the expected incidence in these areas [Hosier D et al 1987]. These resurgences may be explained by periodic shifts in the appearance and resurgence of potent rheumatogenic strains of streptococci, particularly those belonging to the M serotypes once so prevalent in epidemics of rheumatic fever.

The virtual disappearance of rheumatic fever combined with the ageing of the population, has altered the prevalence and character of valvular heart disease in the Europe and North America. Calcific aortic stenosis is now the commonest valve lesion with a reported prevalence of 4.8% in those aged 75-86 [Lindroos M et al 1993]. Non-rheumatic degenerative processes more commonly cause mitral valve disease which usually manifests as mitral regurgitation and rheumatic mitral stenosis is seen less frequently. However, mitral stenosis may still be encountered amongst the elderly population. This is because there is a long latent period between acute rheumatic fever and the development of chronic rheumatic valve disease. Also, patients are presenting with restenosis a number of years after a previous successful surgical mitral valvotomy. Furthermore, the immigration from developing countries has meant that mitral stenosis continues to represent an important clinical entity which should not be overlooked.

### 1.2 Mitral Stenosis: Pathology

Cardiac involvement by rheumatic fever produces a pancarditis invariably associated with the murmurs of valvulitis (Carey Coombs murmur) and is therefore easily diagnosed by auscultation. The infiltration of mononuclear cells leads to formation of Aschoff nodules in the interstitium of the myocardium and these are considered pathognomonic of rheumatic carditis. In the acute stage valve lesions are relatively slight. The initial valvulitis results in verruciform deposition of fibrin along the closing portion of both leaflets, representing mechanical traumatic injury of the swollen leaflets by repetitive closure [Horstkotte D et al 1991]. Progressive scarring may then occur. Approximately 50% of children with rheumatic fever will develop mitral valvulitis. Less often the aortic, and occasionally the tricuspid valves are involved, the relative frequency of involvement being related to the pressure sustained by the valve. The

subsequent development of mitral stenosis is four times commoner in females than males.

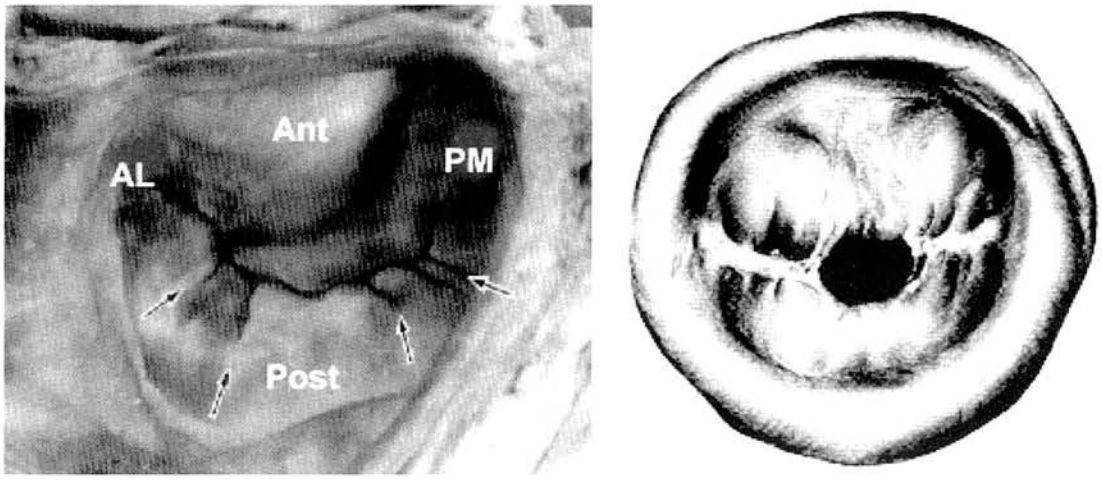
The characteristic feature of chronic rheumatic mitral stenosis is fusion along the line of apposition between the anterior and posterior mitral leaflets (commissure) producing restricted leaflet mobility and fish-mouth shaped orifice with reduced area (Figure 1). Pure commissural fusion with thin, mobile leaflets is seen mostly in younger patients and responds very well to percutaneous valvotomy where the dominant mechanism is commissural splitting [Reid C et al 1987]. Other forms of degenerative change include leaflet thickening and rigidity, tethering and shortening of the chordae tendinae and leaflet calcification.

**Figure 1: mitral valve anatomy**

A. Normal mitral valve anatomy in the closed position viewed from the left atrium. The major commissure (large arrow) is visible between the anterior (Ant) and posterior (Post) leaflets and has anterolateral (AL) and posteromedial (PM) ends. Minor commissures (small arrows) divide the posterior leaflet into scallops

B. Mitral stenosis due to symmetrical bilateral commissural fusion.

**A** **B**



### 1.3 Mitral stenosis: Clinical features

The normal mitral valve area is 4-6 $cm^2$. A reduction in valve area to less than $2cm^2$ is generally required before initial symptoms of exertional dyspnoea become apparent. When the valve area is critically reduced to $<1cm^2$, a considerable left atrial pressure is required to maintain normal cardiac output and pulmonary capillary pressures are elevated at rest causing dyspnoea. Several hours of increased venous return to the pulmonary vasculature which occurs when patients are lying horizontally in bed at night, causes awakening from pulmonary oedema (paroxysmal nocturnal dyspnoea). Cardiac output is usually depressed at rest and fails to rise with exertion producing weakness and fatigue. An increase in heart rate markedly augments the transmitral gradient and left atrial pressure. Therefore, pulmonary oedema can occur precipitously in patients who suddenly develop atrial fibrillation. The increase in blood volume during pregnancy also leads to a raised left atrial pressure and dyspnoea at rest.

Wood [Wood P 1954] differentiated between five forms of haemoptysis complicating mitral stenosis: (1) 'Pulmonary apoplexy' due to sudden rupture of thin walled bronchial veins. (2) Blood stained sputum associated with paroxysmal nocturnal dyspnoea (3) Blood stained sputum complicating chronic bronchitis which occurs commonly in the setting of oedematous bronchial mucosa in patients with mitral stenosis (4) Pink frothy sputum characteristic of acute pulmonary oedema with rupture of alveolar capillaries. (5) Frank haemoptysis due to pulmonary infarction, a late complication of mitral stenosis associated with heart failure.

Systemic thromboembolism from intracardiac thrombus is more likely to occur in patients with mitral stenosis, 80% of whom are in atrial fibrillation. Prior to the advent of surgical and anticoagulant therapy, this serious and disabling complication developed in 20% of patients with mitral stenosis and accounted for one quarter of all fatalities in patients with mitral valve disease [Braunwald E]. Half of all clinically apparent emboli are found in the cerebral vessels but may also involve the coronary circulation leading to myocardial infarction and renal vessels causing hypertension. Rarely, a massive ball-

valve thrombus can occur in the left atrium obstructing mitral inflow. Other complications of mitral stenosis include infective endocarditis and marked left atrial dilatation can lead to hoarseness secondary to compression of the left recurrent laryngeal nerve (*Ortners Syndrome).*

It probably takes a minimum of 2 years after the onset of rheumatic fever for severe mitral stenosis to develop, and in temperate areas a latent period of between 10 and 20 years is usual before the onset of symptoms [Bland E et al 1951]. This may reflect a mild initial carditis causing scarring followed by slow progression of valvar degeneration mediated by non- rheumatic "wear and tear" processes. Alternatively, decades of a "smouldering" rheumatic valvulitis might explain the delay in symptoms [Homer C et al 1951] although this theory is less well supported. A further 5 to 10 years will pass until the patient becomes disabled at which point progression of the disease to death due to pulmonary oedema and pulmonary hypertension with right ventricular failure is relatively rapid. The 5 year survival in medically treated patients is 62% for patients in New York Heart Association (NYHA) symptom class III and only 15% for those in NYHA class IV [Oleson K et al 1962]. Furthermore, a one year mortality of close to 50% has been reported in patients with mitral stenosis developing congestive cardiac failure. [Rapaport E 1975]

### 1.3 Treatment of mitral stenosis: historical development

There are four possible interventions in patients with symptomatic mitral stenosis despite optimal medical therapy: (a) Closed surgical commissurotomy, (b) open surgical commissurotomy, (c) mitral valve replacement and more recently (d) percutaneous balloon mitral valvotomy.

As with pulmonic valvuloplasty, early surgical experience with the treatment of mitral stenosis has paved the way for percutaneous balloon dilatation of the mitral valve. In 1923, Elliot Cutler of Boston reported the first successful operative treatment for mitral

stenosis [Cutler E et al 1923]. In a twelve year old girl he performed a median sternotomy and introduced a curved surgical knife into the left ventricle to cut the diseased mitral valve. The procedure was completed successfully and the patient survived for a further 4 and a half years before dying suddenly. However, surgery had resulted in significant mitral reflux. Believing that mitral regurgitation was tolerated better than stenosis, Cutler operated on a further six patients using similar techniques, but all succumbed.

Two years later, Henry Souttar, surgeon to the London Hospital, performed the first successful mitral valvotomy via the atrial approach [Souttar HS 1925]. In a 19 year old 'thin girl with a bright malar flush' the mitral valve was explored digitally through the left atrial appendage. Although a commissurotomy incision had been planned, Souttar detected an unexpected degree of mitral regurgitation and instead used 'digital separation of adhesions' to dilate the orifice. The patient was symptomatically improved and lived for 5 years before dying from a cerebral embolus. Souttar concluded in his report to the British Medical Journal that 'the method of digital exploration through the auricular appendage cannot be surpassed for simplicity and directness'. However, JH Powers [Powers JH 1932], one of Cutlers' residents, demonstrated conclusively in laboratory animals the disastrous implications of mitral regurgitation superimposed on existing stenosis. Combined with Cutlers own discouraging results, these findings caused British physicians to discontinue direct operations on cardiac valves and Souttar was referred no more patients.

A quarter of a century was to pass before Bailey [Bailey CP 1949] in the USA and Brock [Brock RC 1951] in Britain were to firmly establish closed mitral valvotomy as a valuable surgical treatment. Bailey used finger palpation of the valve followed by commissurotomy with a hooked finger knife. Brock was the chief advocate of digital separation of the fused leaflets and clearly described that that in order to preserve the integrity and function of the valve, 'enlargement of the narrowed orifice must be made along the line of the commissures'. In more severely degenerative valves, finger pressure was not always adequate for dilatation. With the introduction of specially designed transventricular mechanical dilators by Logan, which were further refined by

Tubbs, this problem was overcome and closed mitral commissurotomy became a widely practiced treatment for mitral stenosis. The operation was short, simple and provided good haemodynamic and long term results in patients with mobile, non-calcified valves with pure commissural fusion [Ellis L et al 1973].

Following the advent of safe cardiopulmonary bypass, the closed procedure became replaced in the United States and Europe by open commissurotomy which could be performed more accurately under direct vision. The open technique provided more complete commissural incisions, separation of fused chordae, debridement of calcium and removal of thrombus from the left atrium. Furthermore, if inspection revealed a valve unsuitable for repair, the surgeon could perform mitral valve replacement. Both open and closed techniques were associated with an acceptable mortality rate ranging from 1 to 3 % but open commissurotomy provided better haemodynamic improvement with fewer embolic complications [Farhat M 1990]. The closed procedure remains popular in some developing countries where patients with mitral stenosis are younger with less severe degenerative valve disease and the high cost of cardiac surgery can be avoided.

**Balloon mitral valvotomy (BMV)** was first reported in 1984 as an alternative to cardiac surgery by a Japanese cardiothoracic surgeon [Inoue K 1984]. This technique produces a commissurotomy similar to that achieved by surgery [Kaplan J et al 1987] with comparable results to open and closed commissurotomy [Farhat M 1998]. BMV has the advantage that it can be performed percutaneously under local anaesthetic thereby avoiding general anaesthesia, cardiopulmonary bypass and prolonged hospital stay. Inoue used a novel bilobar rubber-nylon balloon catheter which was introduced via a transeptal approach. The balloon was self-seating and could be progressively inflated. With the use of a single balloon, Inoue performed this technique on six patients. Mean mitral gradient decreased from 18 to 7 mmHg, there was a significant reduction in left atrial pressure and no major complications.

The Inoue catheter became approved in 1994 and until then this technique was overshadowed in Western countries by the use of the traditional cylindrical balloons

adapted from pulmonic valvuloplasty. In 1985, Lock used such cylindrical balloons successfully in eight children and young adults with mitral stenosis [Lock J et al 1985]. Following this, Al Zaibag introduced the use of a double-cylindrical balloon technique. Here a floating balloon catheter is used to cross the mitral valve and two guidewires are positioned in the left ventricular apex. Al Zaibag reported successful valvuloplasty in 7 of 9 patients with severe mitral stenosis [Al Zaibag M et al 1986]. Although effective, the double balloon technique is demanding and carries a risk of left ventricular perforation. The Inoue balloon catheter has since been shown to be safer and easier to use [Chen C et al 1990] and is now the most popular technique worldwide. The transvenous or antegrade approach using transeptal puncture is the most widely used. The transarterial or retrograde approach represents an alternative in rare cases where transeptal puncture is contraindicated.

The most recent development in the field of mitral valvotomy has been the introduction of metallic commissurotomy by Cribier in Paris using a device similar to the Tubb's dilator used during surgical commissurotomy [Cribier A et al 1999]). Cribier's preliminary experience suggests that the device is as effective as balloon commissurotomy. However, the method is more technically demanding and the risk of haemopericardium seems higher because of the device and the presence of a guide wire in the left ventricle. An important advantage of metallic commissurotomy is that the dilator is reusable and therefore of particular value in developing countries where low financial means limit the use of the Inoue balloon.

The efficacy of BMV has been confirmed in trials involving several thousand patients [Cheng CR 1995][Iung B 1996]. The technique is now well established as the treatment of choice for rheumatic mitral stenosis in young patients with pliant, non-calcified valves [Dean LS et al 1994][ Palacios IF 1995][ Chen C et al 1995]. In suitable patients BMV can be expected to provide over 100% increase in valve area, with a final valve area of 2 $cm^2$ on average. The improvement in valve function results in an immediate decrease in left atrial and pulmonary pressures, both at rest and on exercise. Studies of longer term outcome up to 10 years are beginning to creep into the literature and one large series confirms the late efficacy of BMV [Iung B et al in 1999].

With the disappearance of rheumatic fever in the developed world, patients with mitral stenosis presenting to Western centres today are elderly with valves less suitable for BMV but higher operative risk. BMV would have a role in this group of patients if it offered symptomatic improvement sustained for a reasonable period at low procedural risk. The reported experience of BMV in the elderly and those with marked degenerative valve disease is limited and results have been largely unpredictable. Additionally, no randomised studies are available for these patients and a comparison of the results of PMC with those of surgical series is difficult because of the differences in the patients involved. In Edinburgh I have the opportunity to study the benefits of BMV in a large, heterogeneous elderly population. 300 patients were followed up for 1 to 10 years, representing the largest reported long term follow up study in this age group.

## 1.4 Echocardiographic assessment of mitral stenosis

### -Historical development

The first clinical application of cardiac ultrasound was the diagnosis of mitral stenosis. In 1956, Edler and colleagues first documented the distinctive pattern of reflected echos in mitral stenosis. They observed that on the M-mode echocardiogram the normal anterior mitral leaflet closed partially shortly after initial opening to produce an early diastolic "E-F" slope which was steep. In mitral stenosis, this early diastolic closure did not occur or occurred at a much slower rate thereby diminishing the E-F slope (Figure2). This reflected the slower filling of the left ventricle and tendency for the mitral valve to be held open in diastole due to the persistent pressure gradient between the left atrium and left ventricle. In 20 cases selected for commissurotomy, Elder demonstrated that the degree of mitral stenosis found at operation corresponded to the reduced E-F slope and the increased amplitude of movement of the anterior mitral leaflet after valvotomy corresponded to dilatation of the mitral valve. The E-F slope was initially used to quantify the severity of stenosis. However, investigators later found the correlation between E-F slope and the degree of stenosis to be poor and this measurement is no

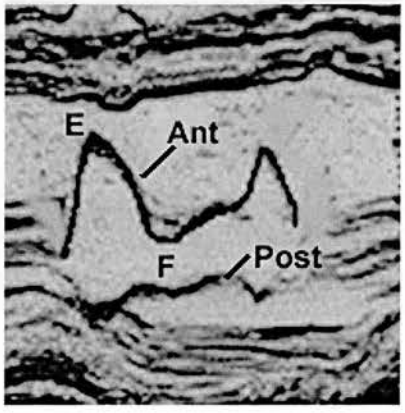
longer used [Nichol P 1977]. Other M-mode characteristics of mitral stenosis include abnormal anterior motion of the posterior mitral leaflet with reduced leaflet separation. This probably reflects commissural fusion such that the leaflets act as a single unit. The M-mode also produces dense lines with multiple echo reflections indicating thickened and calcified leaflets.

**Figure 2. M-Mode of the mitral valve**

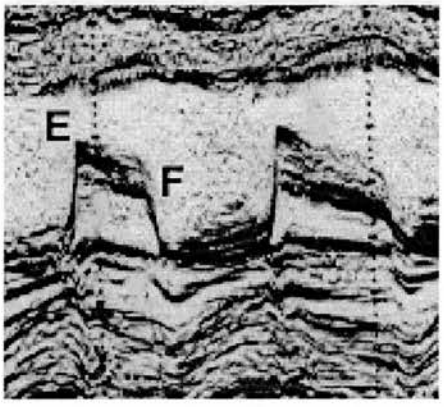
A. M Mode scan of a normal mitral valve showing motion of anterior (Ant) and posterior (Post) leaflets and steep E-F slope.

B. M Mode scan in mitral stenosis showing thickened leaflets and reduced E-F slope

A




B



In the mid-1970s two dimensional sector scanning allowed real time tomographic images of cardiac structures [Tajik A 1978] and provided additional qualitative information in patients with mitral stenosis. The principle diagnostic feature on 2-D echo is doming of the anterior leaflet in diastole. The leaflets may appear thickened and calcified and this may extend into the subvalvular apparatus. The posterior leaflet is relatively immobile and the left atrium is dilated. In the short axis parasternal view, the narrowed orifice appears as a "fish-mouth" and commissural fusion and calcification can be assessed.

The development of Doppler echocardiography paralleled that of M-mode and 2-D echo from the early 1950s, however it was not used clinically until the late 1970s. Doppler echo provided for the first time a non-invasive technique for acquiring haemodynamic data for the quantification of mitral stenosis severity. Utilisation of the Doppler principle also led to the development of colour flow mapping in the early 1980s allowing visualisation of abnormal blood flow and semi-quantitative assessment of mitral reflux.

Transoesophageal echocardiography (TOE) is a newer, semi-invasive imaging modality which is now widely practised. The oesophageal window posterior to the heart provides superior resolution of the mitral valve compared with transthoracic imaging. TOE also allows clear visualisation of the left atrium and its appendage, which are not readily seen from precordial images. TOE therefore has an important role in the detection of left atrial thrombus in patients with mitral stenosis

Three-dimensional echocardiography (3-DE) is an exciting development in ultrasound technology. The concept of 3-D ultrasound was first described by Baum and Greenwood in the early 1960s [Baum G et al 1961]. After obtaining serial parallel ultrasound images of the human orbit, they created a 3-D display by stacking sequential photographic plates bearing the ultrasound images. Since this pioneering work, recent advances in computer technology, digital storage, manipulation and display techniques have meant that 3-DE is now a practical reality. Images can be acquired and reconstructed rapidly and 'real time' transthoracic 3-D probes are already commercially available. The study of mitral valve disease, in particular defining the site and extent of mitral valve prolapse

and assessment of results of balloon mitral valvotomy, has become one of the most promising clinical applications of 3-DE.

### 1.6 Echocardiography in patients undergoing balloon mitral valvotomy

In the 1950s during the era of surgical valvotomy, only physical signs and fluoroscopy were available to predict valve anatomy. Balloon mitral valvotomy was introduced at a time when echocardiography was available to examine the valve in more detail. Valve morphology has been shown to be the strongest determinant of outcome after valvotomy and 2-D transthoracic echo has become the cornerstone of assessment of patients undergoing BMV.

A number of echo scoring systems have been devised which allow classification of patients into anatomic groups with a view to predicting results. Most authors use the Wilkins Score developed at the Massachusetts General Hospital [Wilkins G et al 1988] (Table1). Wilkins assessed four aspects of valve anatomy: leaflet thickening, leaflet mobility, leaflet calcification and subvalvular thickening (figure3). Each is graded on a scale of 0 to 4. Higher Wilkins Scores (>8) indicate more severe degenerative disease and studies have shown this to be associated with lower success rates from BMV and an increased risk of complications [Wilkins G et al 1988][Abascal V et al 1989]. Other investigators like Cormier from Paris use a more general assessment of valve morphology (Table 2).

**Table 1. Wilkins' Echo Score, Massachusettes General Hospital**

| *Grade* | *Mobility* | *Subvalvular thickening* | *Leaflet thickening* | *Calcification* |
|---|---|---|---|---|
| 1 | Highly mobile, only leaflet tips restricted | Minimal thickening just below leaflets | Leaflets near normal thickness (4-5 mm) | Single area of echo brightness |
| 2 | Leaflet mid and base move normally | Thickening of chordae extending to one third chordal length | Mid-leaflets normal, considerable thickening of leaflet margins (5-8mm) | Scattered areas of brightness confined to leaflet margins |
| 3 | Valve moves forward in diastole mainly from base | Thickening extends to distal third of chords | Thickening extends through entire leaflet (5-8 mm) | Brightness extends to mid portion of leaflets |
| 4 | No/minimal forward movement of leaflets in diastole | Extensive thickening and shortening of all chordal structures extending to papillary muscles | Considerable thickening of all leaflet tissue (>8-10 mm) | Extensive brightness throughout much of leaflet tissue |

**Table 2 Cormier's Score. Tinon and Bichat hospitals, Paris**

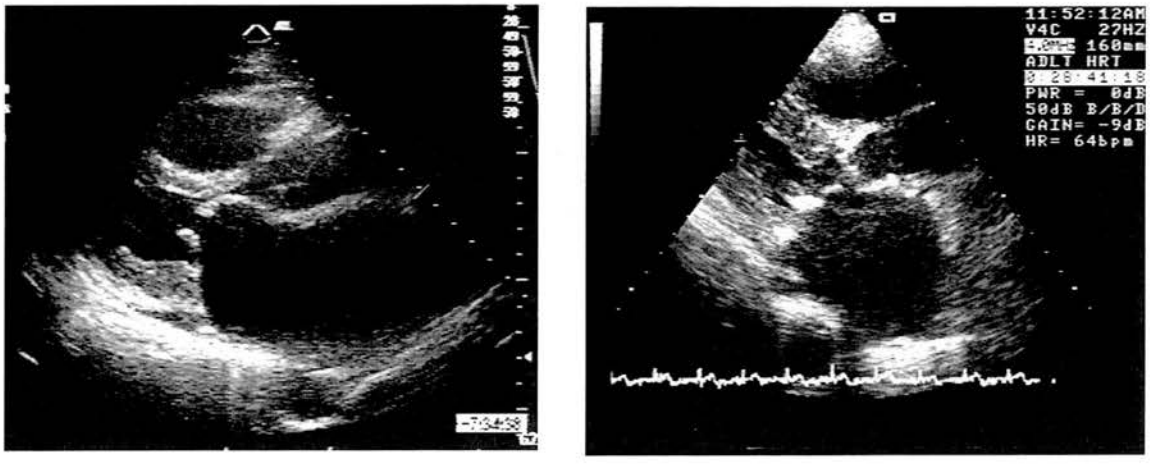
| Echocardiographic group | Mitral valve anatomy |
|---|---|
| Group 1 | Pliable, non-calcified anterior leaflet, mild subvalvar disease (chordae >10mm long) |
| Group 2 | Pliable, non-calcified anterior leaflet, severe subvalvar disease (chordae <10 mm long) |
| Group 3 | Calcification of mitral valve of any extent, as assessed by fluoroscopy, whatever the subvalvar apparatus |

**Figure 3. 2-D Echo illustrating Wilkins Score**

A. Mitral stenosis with low Wilkins Score ('good' valve for balloon valvotomy). Leaflets slightly thickened at the tips, mobile anterior leaflet bows in diastole, no subvalvular thickening, no calcification.

B. Mitral stenosis with high Wilkins Score ('bad' valve for balloon valvotomy). Leaflets are thickened, rigid, heavily calcified with marked subvalvular thickening.

**A** **B**



The work of Kaplan and colleagues using excised human valves, demonstrated the mechanism of balloon dilatation in mitral stenosis to be due to commissural splitting [Kaplan J et al 1987]. They also observed splitting through calcified commissures and suggested that BMV would be efficacious in a wide spectrum of valves including those with heavy calcification. Subsequent clinical studies using transthoracic echocardiography [Fatkin D et al 1993][Cannan C et al 1997] have similarly shown that increase in valve area is achieved by commissural splitting. More importantly, however, calcified commissures resist splitting and strongly predict an adverse immediate and long term result. Assessment of mitral commissural morphology, a feature not included in the Wilkins Score, might improve patient selection for BMV. This is particularly relevant in elderly patients now presenting to Western centres with severe degenerative stenosis, in whom the outcome of BMV has remained largely unpredictable. In a series of 400 patients I report the incidence of commissural calcification, the role of transthoracic echocardiography in its detection and the importance of commissural calcium on outcome after BMV

TOE allows superior resolution of the mitral valve and might offer a further advantage in commissural assessment. This role of TOE has not been previously studied. In a prospective study I have examined the value of TOE in the assessment of commissural fusion and calcification and describe a novel 'Commissure Score' to reflect the likelihood of commissural splitting. I have determined the accuracy of this technique in predicting immediate outcome after BMV.

## 1.7 Measurement of mitral valve area

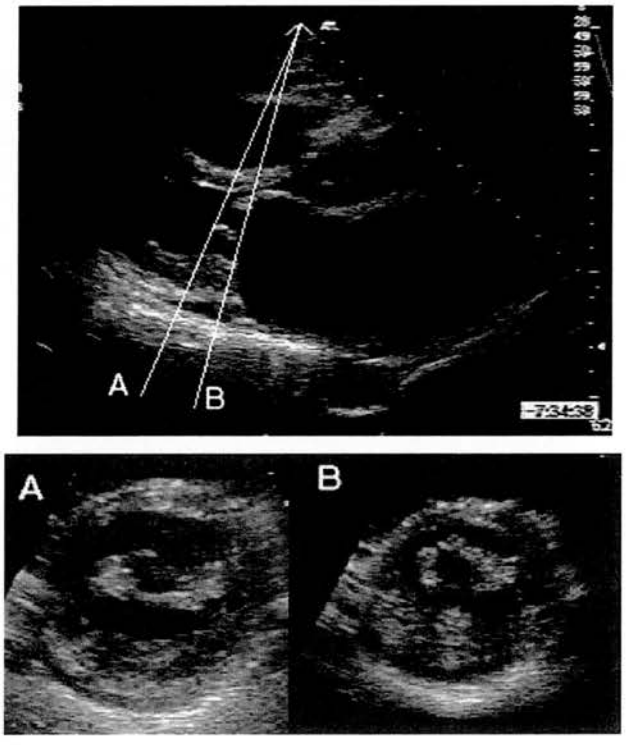
### Limitations of current techniques.

Echocardiography remains the most widely used technique for quantification of mitral stenosis. 2-DE allows direct visualisation of the mitral valve leaflet tips in the short-axis parasternal view where the valve area can be measured by planimetry. However, 2-DE

has the major limitation of visualising the valve in only one image plane which may not be the plane of the orifice (figure 4). Incorrect alignment of the imaging plane characteristically overestimates orifice size [Henry WL et al 1975]. Since the image plane is affected by patient positioning, transducer position and angulation, measurements are subjective and prone to interobserver variability. The results are also dependent on image quality. Rheumatic mitral stenosis is commonly associated with leaflet thickening and calcification and therefore it may be difficult to accurately define the margins of the mitral orifice. Moreover, anterior leaflet calcification causes acoustic shadowing which obscures the mitral orifice. TOE provides improved resolution of the mitral valve and overcomes problems of acoustic shadowing but the same image plane limitations apply to the transgastric short axis view of the valve.

**Figure 4. Limitations of 2-D Echo for planimetry of mitral valve area**

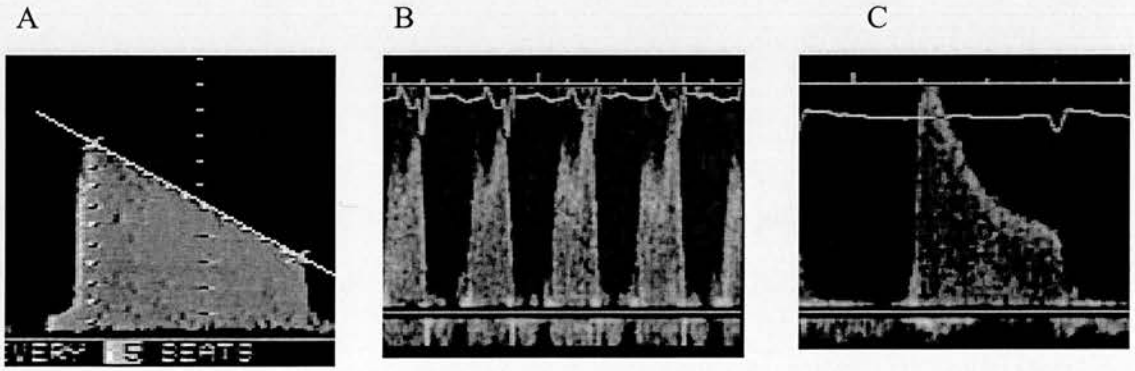
Malalignment of 2-D short-axis image plane cutting through tip of posterior (A) and anterior (B) mitral leaflets. The complete limiting orifice has not been defined.



Doppler echocardiography has been developed as an additional non-invasive technique for quantifying mitral stenosis. The method of Doppler pressure half-time (PHT) was described in 1979 by Hatle and provides a quantitative index of the rate of decay of the diastolic transvalvular pressure gradient from which the valve area can be derived [Hatle L et al 1979]. Doppler tracings are generally easier to obtain and subject to less inter- and intra- observer variability than planimetry. However, difficulty can arise when the diastolic deceleration slope is non linear; mid diastolic flow must be analysed and extrapolated to obtain the initial maximum velocity [Gonzalez M et al 1987]. In patients with sinus rhythm and rapid heart rates the A wave is frequently superimposed on the diastolic slope making measurement of E wave deceleration difficult or impossible (Figure 5). Conversely, in atrial fibrillation, which occurs frequently in mitral stenosis, there can be significant beat to beat variability in PHT measurements [Smith M et al 1991]. PHT measurement is unreliable in the presence of significant coexisting mitral or aortic reflux [Flachskampf FA et al 1990] [Wiesenbaugh T et al 1991], both of which are common in rheumatic valve disease. The PHT method is affected by changes in loading conditions and left atrial and left ventricular compliance. Measurements may therefore be inaccurate in coexisting hypertension or immediately after BMV when there are rapid changes in left atrial pressure and left ventricular filling [Thomas JD et al 1988].

**Figure 5. Limitations of Doppler Pressure Half-Time**

Measurement of pressure-half time is straightforward in (A) but difficult in the presence of sinus tachycardia (B) and when E wave deceleration is non-linear (C).



In selected cases where the severity of stenosis cannot be clarified by echocardiography, for reasons detailed above, catheter derived mitral valve area based on the Gorlin formula [Gorlin R et al 1951] is the widely accepted reference standard. However, this is an invasive technique which is flow dependent and related to the functional rather than the anatomic orifice. Measurements will vary with heart rate, rhythm, changes in LV compliance and severity of mitral reflux [Cohen MV et al 1972]. Left atrial size and function as well as deformity of the mitral valve due to calcification and shortening of the chordal apparatus may all distort flow patterns across the valve and contribute to alterations in Gorlin derived MVA. Following BMV, the Gorlin area may be inaccurate due to the development of significant mitral reflux or presence of an atrial septal defect. Further errors are introduced when the pulmonary artery wedge pressure is used as an indirect measurement of left atrial pressure, or if cardiac output is estimated rather than directly measured [Nakatani S et al 1991].

## 1.9 Three-Dimensional Echocardiography for quantitative and qualitative assessment of mitral stenosis

As yet there is no reliable 'gold standard' for the measurement of mitral valve area. Three-dimensional echocardiography (3-DE) allows cardiac structures to be viewed from any perspective and 2-D cut planes of any orientation can be selected from the 3-D volume data, thereby overcoming the limitations of image plane positioning inherent in conventional 2-D echo. This technique will allow planimetry of the mitral valve area in the optimum plane of the orifice and could provide a 'gold standard' for quantification of mitral stenosis. I report the first *in vitro* study to validate the accuracy of 3-D TOE in the measurement of MVA.

I will also examine the expanding applications of 3-DE in the assessment of mitral valve morphology. From my own experience of this technology, I will describe the benefits and limitations of 3-DE in the assessment of mitral stenosis.

# CHAPTER TWO

## Methods

2.1 Patients

2.2 Data collection and analysis

2.3 Technique of balloon mitral valvotomy

2.4 2-D Echocardiography for the assessment of patients undergoing BMV

2.5 3-D echocardiography

## 2.1 Patients

405 consecutive patients with mitral stenosis underwent BMV between 1986 and 1999 at the Western General Hospital, Edinburgh by a single operator (TRDS). Patients had been referred from hospitals throughout Scotland, 20 were from England and 10 were from abroad. Patients were selected for BMV if echocardiography showed their valve anatomy to be suitable for improvement by commissurotomy or if, regardless of valve morphology, they remained disabled on medical therapy but were high-risk candidates for surgery. The baseline characteristics of these patients are discussed in chapter 3.
In 11 additional patients (2.7%), the procedure was attempted but not completed due to failed transeptal puntcure (2), severe vasovagal reaction (1), balloon unable to cross mitral orifice (5), Haemopericardium (2) and stroke due to dislodged thrombus (1). In two severely ill patients, BMV was performed under general anaesthesia. In 4 cases, BMV was combined with coronary angioplasty.

## 2.2 Data collection and analysis

Clinical, echocardiographic and invasive haemodynamic data for the 405 patients was recorded before and immediately after BMV and documented in the patient records and on a valvuloplasty database (FileMaker Pro). This information was analysed retrospectively. In the 405 patients, values for mitral valve area and mitral regurgitation grade were taken from the invasive catheter data. In concordance with other authors, successful immediate outcome was defined as final MVA>1.5 $cm^2$ without severe MR. The Parsonnet Score [Parsonnet V 1989] was calculated for each patient. This risk stratification method uses objective patient data to predict 30 day operative mortality from open heart surgery.
Longer-term symptomatic follow up data was available for the first 300 patients. Symptom status (New York Heart Association Class) after valvotomy was established by clinic visit or telephone contact. Details of valve replacement and deaths were obtained from general practitioners and referring physicians and Health Board mortality records. Follow up of these 300 patients ranged from 1 to 10 years (mean 25 +/- 2.4

years, median 2.0 years) and was 97% complete (8 patients lost to follow up). Successful long term functional outcome was defined as being alive with sustained symptomatic benefit of at least +1 NYHA class without having been referred for MVR or repeat BMV.

Unless indicated otherwise, data are expressed as mean value +/- standard deviation. Haemodynamic data pre- and post- BMV were compared using the paired Students t test. Non parametric data and binary factors were assessed with respect to outcome using the Mann-Whitney and Chi Squared test, respectively. Differences in the characteristics of the 4 age groups were evaluated using ANOVA. Stepwise multiple linear regression was used to analyse the importance of baseline variables as independent predictors of immediate outcome. Long term symptomatic outcome was presented using the Kaplain Meir method and predictors of long term outcome were determined using Cox Regression analysis. A commercially available statistics package (SPSS version 9 for Windows) was used for all calculations under the supervision of a professional statistician (RE, University of Edinburgh)

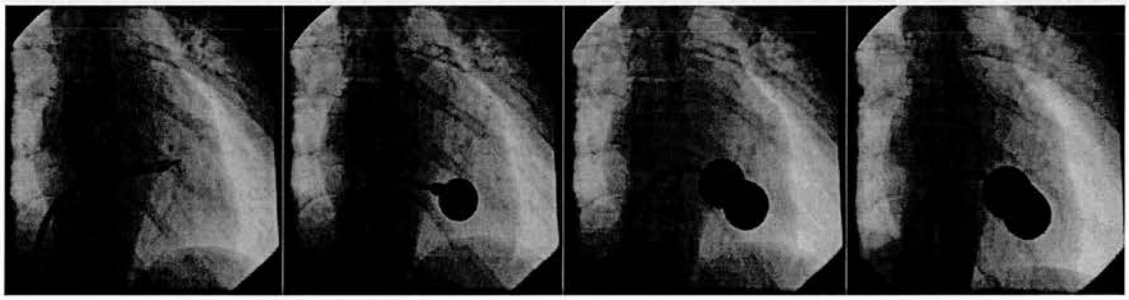
### 2.3 Technique of balloon mitral valvotomy

Patients had been anticoagulated with warfarin for at least 3 months, this was discontinued 3 days prior to admission. BMV was performed in the catheter laboratory under local anaesthesia using fluoroscopic guidance. An 8 French Brockenborough catheter was passed percutaneously from the right femoral vein to the right atrium and, following transseptal puncture, into the left atrium (antegrade approach). A bolus of heparin was administered intravenously.

The first 62 patients were treated by single or double cylindrical balloons based on the methods described by Lock [Lock J et al 1985] and Al Zaibag [Al Zaibag M et al 1986] and in the subsequent cases the Inoue balloon technique was used [Inoue K 1984]. Balloon size was chosen according to the patients' height. The Inoue technique utilizes a catheter with a rubber-nylon balloon which is advanced across the mitral valve into the left ventricle. Following inflation of the distal part of the balloon with contrast, the balloon was pulled back to abut against the mitral orifice and then fully inflated (figure

6). The balloon was progressively dilated to larger diameters. We found both the Inoue and double cylindrical balloon techniques to have the same haemodynamic outcome [Shaw TRD] but there was a shorter procedure time and fewer complications with the Inoue technique.

**Figure 6. Sequential inflation of the Inoue balloon in the left ventricle**



Left ventriculography was performed following each inflation to assess the degree of mitral regurgitation and further inflations were avoided if significant MR developed. Mitral regurgitation assessed by ventriculography was graded from 0-4 using Sellers' classification. Valve calcification was assessed by fluoroscopy and graded as (0) absent, (1) mild, (2) moderate or (3) severe.

Coronary angiography and right and left heart haemodynamic measurements were performed before and after BMV. Cardiac output was calculated by the Fick principal using assumed oxygen uptake and the mean mitral gradient was determined by planimetry from simultaneous left ventricular and left atrial pressure traces. Mitral valve area before and after BMV was calculated using the Gorlin formula [Gorlin R et al 1951]. Coronary angiography was also performed in all patients. Patients were monitored overnight on the cardiac ward, femoral sheaths were removed at 4 hours and they were discharged home the following day if there were no complications

## 2.4 2-D Echocardiography for the assessment of patients undergoing BMV

### 2.41 Transthoracic echocardiography

Prior to BMV, all patients underwent comprehensive 2-D transthoracic echocardiography study using Hewlett-Packard Sonos 2000, Acuson 128 XP/10 or ATL HDI LAB 5000 ultrasound scanners. Two-dimensional, M-Mode, colour and spectral Doppler modalities were utilised.

**Measurement of mitral valve area:**

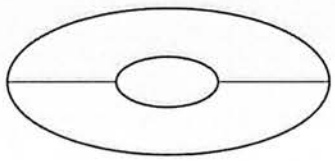
Pulsed Doppler analysis of diastolic trans-mitral flow was performed with the sample volume at the tips of the mitral leaflets in the apical four chamber view and initial mitral valve area (MVA) was derived by the Doppler pressure half time (PHT) method taking the mean value of five recordings. Mitral valve area was also determined by planimetry of the mitral valve orifice in the parasternal short axis view. After BMV, mitral valve area was measured by planimetry the following day or by Doppler PHT at 1 month follow up.

**Assessment of valve morphology:**

The mitral valve leaflet and subvalvular morphology was assessed in the parasternal long axis view and graded according to the Wilkins Score (Appendix 1).

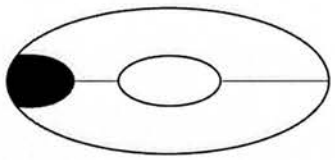
For assessment of the commissures, the mitral valve was examined in the short axis parasternal view. Although by strict terminology the mitral valve has only one commissure between its two leaflets [Anderson RH 1992], I have followed the common convention of considering that the mitral valve has two commissures: posteromedial and anterolateral. The echo beam was scanned repeatedly through the mitral apparatus and the anterolateral and posteromedial commissures of the mitral valve were individually examined. Echocardiographic calcium was identified by high intensity echos. Commissural calcification was said to be present if there was brighter echocardiographic density in the commissures than in the adjacent aortic root. The extent of commissural calcification was quantified by grading each half commissure with such echos as 1. The Commissure Calcification Grade for the valve could therefore range from 0-4 (Figures 7 & 8).

**Figure 7 Grading system for commissural calcification.**



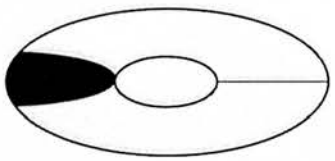
Severe stenosis but no bright echos across either commissure

Grade: 0+0+0+0=0



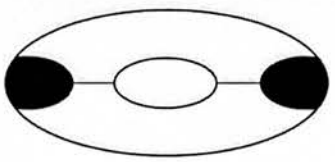
Bright echos extending across one half of posteromedial commissure

Grade: 1+0+0+0=1



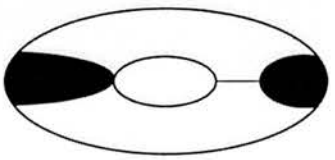
Bright echos extending throughout posteromedial commissure

Grade: 1+1+0+0=2



Bright echos across half of each commissure

Grade: 1+0+0+1=2

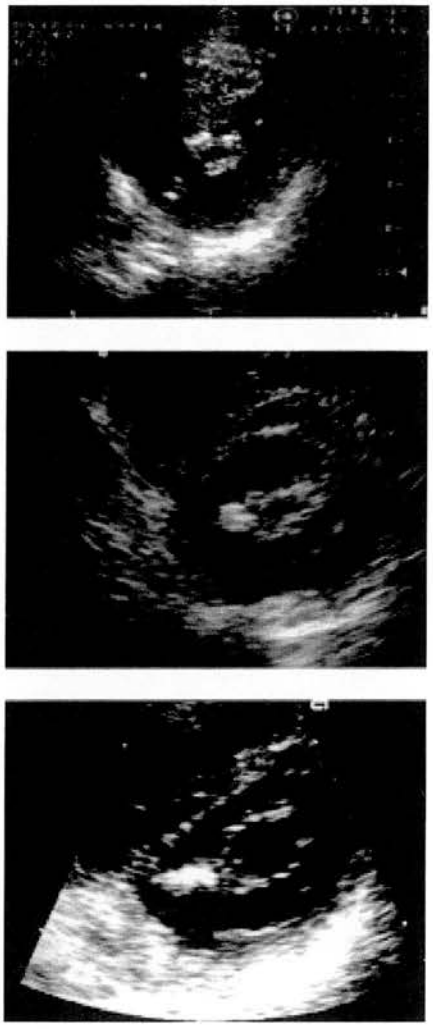


Bright echos across all of posteromedial and half of anterolateral commissure

Grade: 1+1+0+1=3

**Figure 8 Illustrative examples of commissural calcification**.

Upper panel: thickening and brightness at leaflet tips but no bright echoes extending across either commissure; grade 0000 = 0. Middle panel: bright echoes extend across half of posteromedial commissure; grade 1000 = 1. Lower panel: postdilatation the anterolateral commissure has opened well but the posteromedial commissure had bright echoes throughout its length and had resisted splitting; grade 1100 = 2



## 2.6 Transoesophageal echocardiography

The latter 310 patients also underwent transoesophageal echocardiography. TOE was performed immediately prior to BMV following a 4 hour fast using a commercially available 7 MHz multiplane transoesophageal probe and an Acuson 128 XP/10 ultrasound scanner. The pharynx was anaesthetized with xylocaine spray and the examination was performed under intravenous sedation with midazolam. The mitral valve leaflets and subvalvular apparatus were examined at midoesophageal and transgastric levels. The primary role of TOE was to exclude intracardiac thrombus and this required careful imaging of the left atrium, its appendage and interatrial septum.

### TOE assessment of commissural morphology

In a subset of 72 patients TOE was also used to examine the extent of commissural fusion and localization of commissural calcification. The mitral valve commissures were scanned systematically at midoesophageal level. The anterolateral commissure was visualised in the transverse plane by advancing and retracting the probe such that the length of the fused commissure could be scanned from the leaflet tips to the mitral valve annulus. The posteromedial commissure was scanned in a similar manner in the longitudinal plane by rotating the probe clockwise and anticlockwise (Figure 9). Commissural calcification was identified by high intensity echos casting an acoustic shadow (Figure 10). Each commissure was assigned a score to reflect the likelihood of splitting. A score of 0 was given if there was no fusion, or if commissural calcification, expected to resist splitting, was present. When non-calcified fusion was present, a score of 1 was given if the fusion was estimated to extend no more than 5mm from the annulus and a score of 2 given when such fusion extended >5mm from the annulus towards the centre of the valve. Each valve therefore had an overall 'Commissure Score' ranging from 0 to 4, a high score indicating extensively fused, non calcified commissures which were therefore more likely to split, whereas a low score indicated either minimal fusion or the presence of resistant commissural calcification (Table 3).

**Figure 9. Mitral valve anatomy viewed from the left atrium with orientation of the transverse and longitudinal transoesophageal planes**

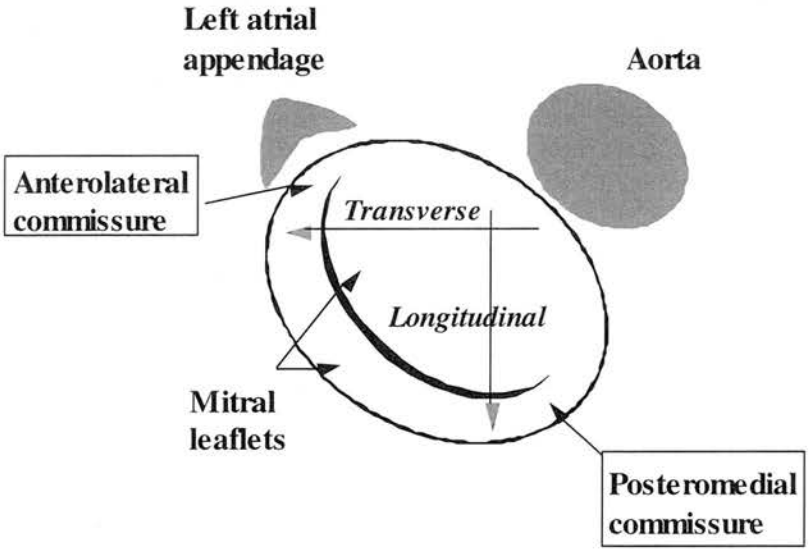



**Figure10 Calcified anterolateral commissure in the transverse midoesophageal plane**

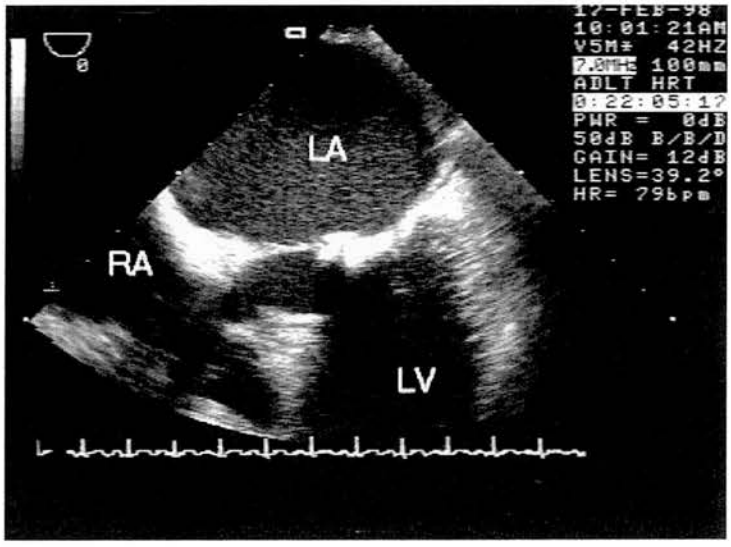


**Table 3** **Commissural scoring system based on transoesophageal echocardiographic assessment**

| Commissure Score | Commissure morphology |
|---|---|
| 0 | Neither commissure fused<br>*or* calcification of both commissures<br>*Or* absent fusion of one commissure, calcification of the other |
| 1 | Partial fusion of one commissure, absent fusion or calcification of the other |
| 2 | Extensive fusion of one commissure, absent fusion or calcification of the other<br>*or* partial fusion of both commissures |
| 3 | Extensive fusion of one commissure, partial fusion of the other, no commissural calcification |
| 4 | Extensive fusion of both commissures, no commissural calcification |

## 2.7 Technique of three-dimensional echocardiography

A three-dimensional data set is composed of anatomical information from multiple static 2-D cross-sectional images which can be obtained from either transthoracic or transoesophageal windows. These images are acquired in a sequential manner along or around an axis, or using reference views. More recently, real time acquisition has been performed by rapidly scanning through a pyramidal volume. For reconstruction of the mitral valve, transoesophageal echocardiography is the preferred approach since it offers a stable transducer location from which high resolution images of the mitral valve can be acquired thereby improving the quality of the 3-D display.

The multiplane TOE probe is rotated at 2 or 3 degree increments over 180 degrees and 90 or 60 sequential 2-D cross sections are digitised to form a conical data set [Salustri A et al 1995]. Optimal temporal and spatial registration is achieved by ECG and respiratory gating. Off-line processing involves the conversion from polar to cubic Cartesian co-ordinates and interpolation of missing information between 2D slices. From the resultant data set, novel 2-D cut planes in any orientation can be selected (anyplane echo) and multiple parallel cross-sectional 2D slices can be generated in any desired plane (paraplane echo). A volume rendered 3-D image of the mitral valve can be reconstructed from any perspective. This allows a full appreciation of the complex geometry and spacial relationships of the mitral valve. Threshold limits are used to separate cardiac structures from blood pool and background. Brightness and shading provide perception of depth. With the added dimension of time (four-dimensional echocardiography) we are able to study in detail the motion of the valve during the cardiac cycle.

## 2.7 Study limitations and sources for error

This study included only patients referred for consideration for mitral balloon valvotomy and does not reflect the characteristics of all patients with mitral stenosis. Relatively fit patients with markedly degenerate mitral valves may have been referred by their

cardiologist direct for cardiac surgery. Other frail patients with severe mitral stenosis who were sufficiently controlled on medical treatment may not have been referred to the cardiac centre for consideration of balloon valvotomy.

Echocardiographic evaluation of commissural calcification and Wilkins criteria by multiple observers is subjective and exposed to variability. The inferior resolution offered by earlier echo machines would have made assessment more difficult and on occasions inaccurate. Bright echoes on the valves are taken to represent calcification but may also be caused by dense fibrosis; a study of the correlation between echo appearances and pathological findings would be required to confirm this assumption.

Immediate haemodynamic data was based on invasive measurements derived by the Gorlin formula. Although this is generally regarded as the 'gold standard' and used by most investigators, the Gorlin area is less reliable during changes of heart rate and loading conditions which occur during valvuloplasty and further errors are introduced when cardiac output is estimated (as in our own centre) rather than measured directly.

# CHAPTER THREE

# Characteristics of 405 patients undergoing BMV and comparison between four age groups.

## 3.1 Background

Reported series of BMV have been described mainly in young patients with pliable, non-calcified valves. Since the disappearance of rheumatic fever in the Western World, the characteristics of patients now presenting with symptomatic mitral stenosis to centres such as ours has changed dramatically. The population is heterogeneous, patients tend to be older and many have adverse valve morphology and significant comorbidity. There is currently little data in the literature on the clinical and haemodynamic characteristics of this population and this information is of interest to Western centres involved in the selection of patients for BMV.

## 3.2 Aims

To evaluate clinical and haemodynamic characteristics of 405 patients undergoing BMV at one high volume UK regional centre and to compare these within four age groups (>40, 40-54,55-69,>70).

## 3.3 Patients and methods

See section 2.1. Four hundred and five consecutive patients with mitral stenosis underwent BMV. Baseline clinical, echocardiographic and invasive haemodynamic data were collected over a 13 year period. This data was documented in the patient records and valvuloplasty database and I analysed these retrospectively.

## 3.4 RESULTS

**Table 4. Baseline characteristics of 405 patients**

| | |
|---|---|
| Age (years) | 60.7 +/- 12.5 |
| Female | 79% |
| Atrial fibrillation | 72% |
| History of rheumatic fever | 39% |
| Previous valvotomy | 22% |
| | |
| NYHA Class | |
| I | 0.5% |
| II | 26.4% |
| III | 48.6% |
| IV | 24.4% |
| | |
| Coexisting Aortic valve disease | 17% |
| Coexisting mitral reflux | 35% |
| LV impairment | 11% |
| Coronary artery disease | 22% |
| RV systolic pressure (mmHg) | 52.8 +/- 19.4 |
| Parsonnet Score | 15.1+/- 8.6 |
| Wilkins Echo Score | 6.6+/-2.9 |
| Fluoroscopic calcification: | |
| None | 58% |
| Mild | 18.3% |
| Moderate | 8.9% |
| Severe | 14.8% |

**Baseline Characteristics**

Table 4 describes the baseline characteristics of the 405 patients undergoing BMV. Our population was elderly with a mean age of 60.7, range 13 to 87. 112 patients (27.7%) were aged 70 and above, 20 patients (4.9%) were octogenarians. The majority were female and in atrial fibrillation. 22% had developed mitral restenosis following a previously successful surgical or percutaneous valvotomy. These 405 patients had severe symptomatic mitral stenosis with a mean pre- valve area of 0.93 +/- 0.3 $cm^2$ and 73% were in NHYA class III or IV. Medical and cardiac comorbidity was common. The Parsonnet Score [Parsonnet V 1989] predicted the mean 30 day operative mortality from mitral valve surgery at 15.1%. Twenty six percent of patients had been judged to be unsuitable for surgery by either the referring physician or cardiac surgeon. The reason for unsuitability for operation was additional severe inoperable, non-mitral disease in 8, severe pulmonary disease in 33 and frailty and/or medical comorbidity in 67. The commonest medical problems were renal failure, chronic neurological disability, malignancy, severe arthritis, morbid obesity, diabetic complications and moderate cardiac or pulmonary disease. Frequently several medical problems co-existed.

A significant number of patients had severe degenerative valve disease: one third had a Wilkins Echo Score of 8 or more which would predict a poor outcome from BMV. Moderate or severe fluoroscopic calcification was present in 23.7%. The latter 310 patients underwent transoesophageal echocardiography prior to BMV. Intracardiac thrombus was detected in 41 cases (13.2%), all but one of these patients had been anticoagulated with warfarin.

**Baseline characteristics according to age groups**

Of the 405 patients, 19 (4.7%) were aged <40, 101 (24.9%) aged 40-54, 173 (42.7%) aged 55-69 and 112 (27.7%) were 70 years and above. Baselines clinical and haemodynamic characteristics of these 4 age groups are shown in Table 5.

**Table 5 Baseline characteristics of patients in four age groups**

| | **<40 yrs** (n=19) | **40-54 yrs** (n=101) | **55-69 yrs** (n=173) | **70+ yrs** (n=112) | P value (ANOVA) |
|---|---|---|---|---|---|
| Female (%) | 79 | 76 | 77 | 85 | 0.32 |
| Atrial fibrillation (%) | 21 | 59 | 77 | 85 | <0.001 |
| NYHA class | 2.53+/-0.7 | 2.71+/-0.7 | 2.93+/-0.7 | 3.34+/-0.64 | <0.001 |
| Previous valvotomy (%) | 5 | 23 | 25 | 18 | 0.14 |
| Parsonnet Score | 10.2+/-5.6 | 10.0+/-5.1 | 12.5+/-5.3 | 24.6+/-8.4 | <0.001 |
| Inoperable (%) | 0 | 5 | 21 | 59 | <0.001 |
| Pre-MR (%) | 26 | 27 | 35 | 44 | 0.09 |
| Fluoroscopic Calcium (%) | 5 | 19 | 44 | 60 | <0.001 |
| Wilkins Echo Score | 4.42+/-1.8 | 5.47+/-2.4 | 6.72+/-2.83 | 7.92+/-3.1 | <0.001 |
| Pre-RV pressure (mmHg) | 54+/-21.4 | 49.3+/-19.5 | 52.5+/-18.1 | 56.2+/-20.5 | NS |
| Pre-area ($cm^2$) | 0.99+/-0.3 | 0.96+/-0.3 | 0.94+/-0.3 | 0.86+/-0.27 | <0.05 |
| Pre-mean LA (mmHg) | 25.6+/-8.2 | 25.1+/-6.9 | 24.9+/-6.9 | 25.0+/-7.0 | NS |
| Pre-mean Gradient (mmHg) | 18.9+/-8.3 | 13.2+/-4.6 | 12.3+/-4.9 | 11.4+/-4.7 | <0.001 |
| Cardiac Output (l/Min) | 4.7+/-1.1 | 3.9+/-0.9 | 3.6+/-0.9 | 3.3+/0.8 | <0.001 |
| LV impairment (%) | 5 | 4 | 15 | 13 | 0.05 |
| Coronary artery disease (%) | 0 | 5 | 23 | 62 | <0.01 |
| Aortic valve disease (%) | 11 | 17 | 16 | 23 | NS |
| Left atrial thrombus (%) | 0 | 8 | 14 | 23 | <0.05 |

Right ventricular and left atrial pressures were similar between age groups. Younger patients had less severe mitral stenosis, although cardiac output was higher resulting in an increased mean transmitral gradient compared with older patients.
Severity of stenosis increased with age and was paralleled by increased symptomatic limitation (NYHA Class). Older age groups were less likely to remain in sinus rhythm, were at increased risk of intracardiac thrombus and had greater comorbidity including coronary artery disease. The Parsonnet risk scores in these elderly patients were therefore higher and far fewer had been judged fit for mitral valve replacement. Echocardiographic and radiological appearances showed that older patients also had more severely deformed and calcified valves. Fluoroscopic valvular calcification was moderate or severe in 43% of those over 70 compared with 22% of the under 70s. Of those over 70 years, 55% had a Wilkins Score of 8 or more compared with 26% of those under 70. Older patients were therefore less likely to have an optimal increase in MVA from balloon dilatation.

**3.5 Discussion:**

Since the disappearance of rheumatic fever in the Western world, patients with mitral stenosis presenting to centres such as our own are typically elderly. Other large published series have generally included younger patients with mean ages ranging from 38 to 54 years [Chen C et al 1995][Iung B et al 1996][Dean L et al 1996]. Our population had a mean age of 60.7 years with 22% having developed restenosis after a previous successful surgical valvotomy. These patients are on average 24 years older than those who underwent surgical mitral valvotomy at our hospital when the operation was introduced in the 1950s. In the 1930s it was found that of patients with mitral valve disease 61% were aged under 40 [Wood P 1968] compared with 6% in our series.

A number of clinical features of mitral stenosis have changed since Paul Wood reviewed his experience of mitral valve disease in the early 1950s [Wood P 1954]. A history of rheumatic fever is now less common than the 68% noted by Wood. In his series of 300

patients, 83 had pregnancies associated with mitral stenosis compared with only one of our 405 patients. He found an 18% incidence of severe haemoptysis while this was reported in 2 (0.5%) of our patients. As most of our patients came from other cardiac centres we did not have an accurate record of incidence of systemic embolism but it appeared much lower than the 66% incidence in Wood's patients who had atrial fibrillation. At operation 23% of his patients had left atrial thrombus which was much higher than we found at transoesophageal echocardiography (warfarin was not available at that time but was used by 95% of our patients).

I compared four age groups and illustrated the marked affect of age on the clinical and haemodynamic characteristics of patients with severe mitral stenosis undergoing BMV. Elderly patients undergoing BMV have more severe and symptomatically limiting stenosis. A low cardiac output state in the elderly resulted in a lower mean transvalvular gradient despite more severely narrowed valves; this should be taken into account when assessing stenosis severity at cardiac catheterisation. Older patients have more severely thickened and calcified valves indicated by the Echo Score and fluoroscopy. Also, as age increases, atrial fibrillation is more common and there is a higher incidence of atrial thrombus. BMV is therefore an unattractive option in these patients and mitral valve surgery would normally be considered. However, this group would have an increased mortality from mitral valve surgery predicted by the Parsonnet Score. This is the most widely accepted system for estimating 30 day operative mortality from cardiac surgery which assigns a 7% risk for patients aged 70-74, 12% for those aged 75-79 and 20% for octogenarians. Surgical data confirm that mitral valve replacement is associated with high morbidity and mortality in the elderly and carries a much higher risk than aortic valve surgery. However, these series include predominantly patients with mitral regurgitation secondary to papillary muscle dysfunction complicating ischaemic heart disease where mortality is approximately 20% [Davis EA et al 1993], increasing to 50% if combined with coronary artery bypass grafting [Tsai TP et al 1986]. No large-scale studies of mitral valve surgery for pure mitral stenosis are available. It is of interest that 59% of patients aged 70 and over were judged to be inoperable by the referring

physician or cardiac surgeon due to comorbidity or frailty, compared with only 14% of those under 70. BMV might therefore be the only available therapeutic option in many elderly patients, but could be justified only if it was safe and offered symptomatic benefit.

# CHAPTER FOUR

## Immediate outcome in 405 patients and comparison between four age groups.

### 4.1 Background

Since its introduction in 1984, balloon mitral valvotomy has been used extensively and its safety and immediate efficacy has been well documented [Chen C et al 1995][Iung B et al 1996][NHLBI Registry 1992]. Prospective randomised trials have shown that BMV produces immediate haemodynamic, echocardiographic and symptomatic results at least as good as those obtained by surgical commissurotomy. [Farhat M et al 1990][Reyes V 1994]. However, these studies are described in young patients with pliable, non-calcified valves. There is less experience of the safety and outcome of BMV in older patients with adverse valve anatomy and comorbidity and few studies have compared BMV in diverse patient subsets. This information would be of value to Western centres dealing with a predominantly older patient population and might improve case selection.

### 4.2 Aims

1. To assess the safety of BMV in a heterogeneous population.

2. To analyse immediate haemodynamic and 3 month symptomatic outcome and to compare these within the 4 age groups.

3. To identify predictors of immediate outcome.

### 4.3 Patients

(See section 2.1). 405 patients undergoing BMV at one high volume tertiary centre by a single primary operator (TRDS). Clinical and haemodynamic data was analysed

retrospectively from patient records and the valvuloplasty database. Baseline characteristics have been described in chapter three

## 4.4 RESULTS

### 4.41 Complications

Of 416 patients in whom valvotomy was attempted (405 completed, 11 incomplete), severe complications occurred in 17 patients (4.1%).

One patient died during the procedure (0.2%): she developed cardiac tamponade from LV perforation by a cylindrical balloon. Two other patients developed tamponade but underwent successful surgical repair. Two patients aged 65 and 69 died at 2 and 3 days post-BMV; one from a severe stroke which developed during the valvotomy and one from complications of lupus erythematosus and cerebrovascular disease. Embolic events occurred in 7 patients (1.7%). Two had transient foot ischaemia, 3 developed evidence of coronary embolism, 1 had transient diplopia and 1 had persistent hemiparesis. All were over 60 years of age. Five patients developed severe mitral regurgitation requiring valve replacement, although none required emergency surgery. Although many of the elderly patients were unwell and sometimes moribund, they tolerated BMV well. No other patients developed cardiogenic shock, acute pulmonary oedema, newly sustained atrial or ventricular arrhythmia or required a vascular repair procedure.

A further 117 patients (29%) developed less severe complications. Most common of these was left to right interatrial shunt. Significant shunting (Qp/Qs >1.5:1) was detected by oximetry in 12 patients (3%). 24 patients (6%) developed moderate mitral regurgitation. Other minor complications included transient arrhythmia, hypotension and syncope. The development complications could not be predicted from any of the baseline variables. Embolic events were confined to the older age groups (range 61-82 years). The number of patients alive and free from MVR was 97.3% at 3 months, falling to 86.4% at one year.

### 4.42 Immediate haemodynamic and symptomatic results

**Table 6 Haemodynamic and symptomatic data pre- and post- BMV in 405 patients.**

| | Before BMV | After BMV | P value |
|---|---|---|---|
| MVA ($cm^2$) | 0.93+/-0.3 | 1.7+/-0.7 | <0.01 |
| Transmitral gradient (mmHg) | 12.6+/-5.2 | 5.7+/-2.9 | <0.01 |
| Cardiac output (l/min) | 3.6+/-1.0 | 4.4+/-1.5 | <0.01 |
| NYHA class | 2.97+/-0.73 | 1.9+/-1.0 | <0.01 |
| Mean LA pressure (mmHg) | 25.0+/-7.0 | 20.4+/-7.3 | <0.01 |

Data pre- and immediately post- BMV are shown in table 6. Immediately after BMV, MVA and cardiac output increased, mean transvalvular and LA gradient was reduced and NYHA class at 3 months was improved (all $p<0.01$). 58.8% obtained a final MVA>1.5 $cm^2$ without severe mitral regurgitation (successful haemodynamic outcome). At 3 months, 80.7% of the 405 patients were improved by at least 1 NYHA class, 6 patients (1.5%) had undergone valve replacement and 5 (1.3%) had died.

The older groups also achieved a significant immediate haemodynamic improvement although this was less pronounced compared with younger patients (table 7). There was a trend toward a larger increase in valve area and cardiac output in the younger groups, although this did not reach significant levels. Younger ages achieved a greater reduction in mean transmitral and left atrial pressure gradients after BMV. Patients achieving a successful haemodynamic outcome (MVA>1.5 without significant MR) included 79% of those aged <40, 63% of those aged less than 70 and 48% of those over 70 ($P<0.02$). The elderly were more severely symptomatically limited at baseline but all age groups obtained a significant improvement in NHYA class at 3 months. Indeed, the degree of symptomatic improvement indicated by increase in NYHA Class was greater in the older age groups. The incidence of serious complications was not increased in these older patients.

**Table 7 Immediate outcome in 4 age groups**

| | **<40 yrs** (n=19) | **40-54 yrs** (n=101) | **55-69 yrs** (n=173) | **70+ yrs** (n=112) | P Anova |
|---|---|---|---|---|---|
| Post-MVA ($cm^2$) | 2.04+/-0.78 | 1.86 +/- 0.76 | 1.73+/- 0.64 | 1.6 +/- 0.63 | <0.01 |
| Increase MVA ($cm^2$) | 1.05+/-0.69 | 0.89+/-0.62 | 0.79+/-0.54 | 0.74+/-0.5 | 0.054 NS |
| Increase Cardiac Output (l/min) | 1.24+/-1.87 | 0.78+/-0.82 | 0.66+/-0.75 | 0.75+/-1.17 | 0.096 NS |
| Decrease in mean gradient (mmHg) | 11.58+/-6.36 | 7.20+/-4.37 | 6.66+/-4.09 | 5.99+/-3.56 | <0.001 |
| Decrease in LA pressure (mmHg) | 10.74+/-7.38 | 5.19+/-6.25 | 4.17+/-5.68 | 3.59+/-5.56 | <0.001 |
| Increase in NYHA Class | 1.28+/-0.46 | 1.57+/-0.82 | 1.74+/-0.95 | 2.21+/-0.86 | <0.001 |
| MVA >1.5, no MR (%) | 79 | 66 | 60 | 48 | <0.02 |
| Alive,+1NYHA no MVR (%) | 89 | 79 | 80 | 80 | 0.84 NS |

### 4.43 Predictors of outcome in 405 patients:

Variables predicting immediate haemodynamic success are listed in tables 8 (univariate analysis) and 9 (multivariate analysis). Univariate analysis included 21 baseline patient variables of which only 6 were not linked to immediate results: history of rheumatic fever, previous valvotomy, presence of coexisting aortic valve disease, coronary artery disease, LV impairment and balloon catheter type (double cylindrical vs Inoue). A highly significant relation with poor outcome was seen with haemodynamic indicators of severe stenosis (smaller pre-area, higher mean gradient and RV systolic pressure), clinical variables (increased age, female sex, atrial fibrillation) and markers of severe degenerative valve disease (X Ray calcification and higher Wilkins Score). Visualisation of fluoroscopic calcification is a crude method for assessing valve morphology but correlates well with outcome from BMV (Table 10).

**Predictors of immediate haemodynamic success in 405 patients:**

**Table 8 Univariate analysis**

| Baseline Variable | t | P value |
|---|---|---|
| Pre-area | 11.3 | <0.001 |
| Pre-cardiac output | 8.7 | <0.001 |
| XRAY calcium | -6.4 | <0.001 |
| Echo Score | -6.3 | <0.001 |
| Pre-RV systolic pressure | -5.8 | <0.001 |
| Parsonnet Score | -4.7 | <0.001 |
| Operable | 4.0 | <0.001 |
| Pre-mean mitral grad | -3.7 | <0.001 |
| Age | -3.7 | <0.001 |
| AF | -3.6 | <0.001 |
| Female | -3.6 | <0.001 |
| Pre-NYHA | -3.5 | <0.001 |
| Pre-mean LA grad | -3.0 | <0.01 |
| Pre-MR | -2.2 | <0.05 |

**Table 9 Multivariate analysis**

| Baseline Variable | P value | Odds Ratio |
|---|---|---|
| Pre-area | <0.001 | 1.79 |
| Female | <0.01 | 0.85 |
| Xray Calcification | <0.02 | 0.94 |
| AF | <0.02 | 0.91 |

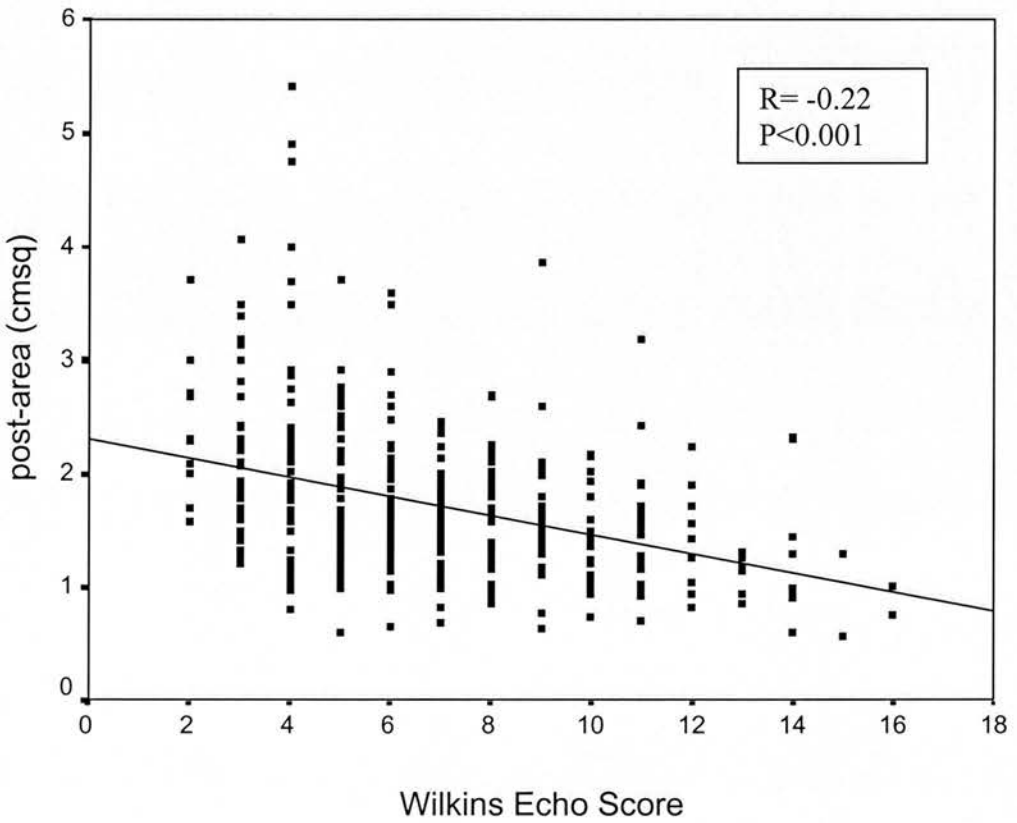
**Table 10. Influence of fluoroscopic calcification on immediate outcome of BMV.**

| Fluoroscopic Calcification Grade | Increase in MVA (cmsq) | MVA >1.5 cmsq, no severe MR |
|---|---|---|
| 0 | 0.9+/-0.61 | 70 % |
| 1 | 0.79+/-0.5 | 62 % |
| 2 | 0.67+/-0.48 | 42 % |
| 3 | 0.63+/-0.38 | 25 % |

**Wilkins Score and Outcome**

Figure 11 shows the correlation between Wilkins Score and increase in valve area ($r=-0.22$, $p<0.001$). Although this was significant, there was substantial scatter in the data; a third of those with a low score still had a poor result. Using the conventional cut-off of 8, a Wilkins score of 8 or less predicted a good outcome with a both sensitivity and specificity of approximately 65%. Analysis of the four individual Wilkins factors showed that all were significantly related to immediate outcome. Leaflet calcification was the most powerful predictor and a stronger correlation was obtained when the four factors were combined rather than used individually.

**Figure 11. Correlation between Wilkins Echo Score and immediate outcome from BMV**



The forth and final multivariate logistic model included four variables (table 9). The strongest independent predictor of immediate haemodynamic success was initial valve area[1]. Males[2] and those in sinus rhythm[3] were more likely to have a successful outcome. Mitral valve calcification identified by fluoroscopy[4] predicted an adverse outcome.
The severity of stenosis progressed in parallel with degenerative disease of the leaflets and subvalvular apparatus and therefore those with a smaller initial valve area had a higher Wilkins Echo Score. When pre-catheter variables only are included in the multivariate model (pre-area therefore removed), Echo Score emerged as an independent predictor of outcome.

## 4.5. Discussion:

### 4.51 Complications

BMV was well tolerated, even in the frail elderly. The overall incidence of severe complications was 4.1% and showed a tendency to increase with age. The mortality from BMV was much lower than the 15% predicted mortality from cardiac surgery and compares favourably with the reported procedural mortality of 0-3%.

One of the most devastating complications of BMV is systemic embolism which is reported to occur in 0.5-5% of cases. Embolism is likely to arise from left atrial thrombus and often involves the cerebral circulation. Seven of our 405 patients (1.7%) suffered systemic embolism during or within 48 hours of the procedure. All were over 60 years of age and this is reflected by the higher incidence of left atrial thrombus and atrial fibrillation in this age group.

Cardiac perforation is a major cause of mortality in patients undergoing BMV and may be a result of atrial puncture during transseptal catheterisation or from LV perforation by guidewires. Haemopericardium occurs in 0.5-12% of cases in reported series. The single death during BMV in this series was caused by LV perforation and occurred early in our

experience when the double cylindrical balloon was used. The newer Inoue balloon avoids guidewire manipulation in the LV and compared with single- or double-balloon techniques, cardiac perforation with the Inoue technique is much less common (<2% vs 4%) [Bassand J et al 1991].

The development of new or increased MR is a well recognised complication of BMV. A significant increase in MR was seen in 27 (6.5%) of our patients, although this was severe in only 5 (1.2%). The creation of new or increased MR is reported to occur in as many as 19 – 85% of patients and is severe in 3-10% [NHLBI Registry 1992][Essop M et al 1991]. Mild MR commonly occurs at the sites of commissural splitting. Severe MR is usually due to non-commissural tearing of the mitral valve leaflets and less commonly damage to the subvalvular apparatus. Although the need for urgent surgery (within 24 hours) is rare, it may be required for massive haemopericardium or severe mitral regurgitation with haemodynamic collapse or refractory pulmonary oedema. In those escaping emergency valve replacement, significant MR confers an adverse short-term prognosis; 6 of the 27 patients (22%) in our series developing moderate or severe MR either died or required a mitral valve replacement within 3 months, compared with only 1.3% of those without significant MR. However, I was unable to predict the development of complications including MR from baseline anatomical, clinical or haemodynamic variables. The NHLBI investigators showed overall complication rate to be increased in those with smaller pre-MVA and higher Echo Score, but prediction of MR remained elusive. Padial [Padial et al] investigated 566 patients undergoing BMV of whom 37 (6.6%) developed severe angiographic MR. Again, standard baseline characteristics including the Wilkins Score could not reliably predict MR. However, they developed a novel score based on the combined echocardiographic assessment of valvular thickening and calcification, degree and symmetry of commissural disease and subvalvular disease which emerged as the only independent predictor of severe MR with positive and negative predictive accuracy of 77% and 85% respectively.

The occurrence of an atrial septal defect during BMV is a well recognised feature of the antegrade approach where transseptal puncture is required. The frequency of defects

depends on the method used for detection. Transoesophageal echocardiography is the most sensitive technique and detects shunting of various degrees in almost all patients [Arora], these are generally small and undergo spontaneous closure. Oximetry detects shunting in up to 20% of patients but these are significant (ratio > 1.5:1) in fewer than 5% (3% in our series). Even such large shunts improve, particularly in the presence of maintained optimal valve enlargement and are rarely of clinical consequence [Cequier et al 1990]. They do, however, influence the invasive mitral valve area measurements and account for discrepancies between results obtained haemodynamically and by echocardiography [Manga P et al 1993]

### 4.52 Immediate outcome

Our results are in agreement with the literature, demonstrating the efficacy of BMV to provide immediate functional and haemodynamic improvement. Catheter laboratory data indicated a significant increase in mitral valve area and cardiac output and reductions in transvalvular and left atrial pressure gradients. Mitral valve area increased by an average of 117% from baseline. 58.8% of patients obtained a final MVA>1.5 $cm^2$ without significant mitral regurgitation. At 3 months, 80.7% were alive and symptomatically improved. Greatest haemodynamic benefit was seen in the youngest patients: Those aged under forty obtained an average increase in valve area of 152% to a mean final valve area of approximately 2 cmsq and 79% achieved a valve area of > 1.5 without MR. Older patients obtained a significant improvement in MVA (average increase 100%) and cardiac output despite their unfavourable valve morphology. However, this increase in area tended to be less impressive than younger patients and their valves tended to be more severely stenosed at baseline; consequently only 49% of the over 70s achieved a final area of >1.5 cmsq. However, even a suboptimal haemodynamic result in these severely limited patients resulted in useful symptomatic benefit indicated by NYHA class. Indeed, symptomatic outcome at 3 months was not significantly different

in the age groups with 82.6% of the under 70s and 80% of the over 70s achieving a successful symptomatic result.

### 4.53 Prediction of immediate results

Prediction of immediate results was multifactorial, and based on both anatomic, clinical and haemodynamic variables. In the 405 patients, multivariate analysis showed pre-valve area, female sex, X-ray calcification and atrial fibrillation to be independent predictors of immediate haemodynamic outcome.

Valve area before BMV was the strongest predictor. As we would expect, those with more severe stenosis at baseline were less likely to achieve a final valve area of >1.5. Other studies have also found smaller pre-MVA to be a highly significant predictor of haemodynamic outcome and 30-day mortality [Iung B et al 1996][NHLBI Registry 1992].

I found female sex to be a strong independent predictor of poor haemodynamic result; 55% of females had a successful outcome compared with 75% of males. Females were of a similar age to males and had a similar Echo Score, however they generally presented with more severe stenosis ($p<0.01$) and worse NYHA symptom class ($p<0.01$) compared with males.

Atrial fibrillation was an independent predictor of adverse immediate outcome and was a marker for adverse clinical and morphological features. Compared with those in sinus rhythm, patients in AF tended to be significantly older (63.2+/-11.2 vs 54.2+/-13.3 years) with more severe stenosis (0.89+/-0.28 vs 1.01 +/- 0.33 cmsq) and lower cardiac output (3.4+/-0.8 vs 4.3+/-1.0 l/min) – all $p<0.001$. Patients in AF had a higher incidence of previous valvotomy (24% vs 29%, $P<0.05$). They also had more severe degenerative valve disease indicated by fluoroscopic calcification score (089+/-1.14 vs 0.59+/-1.0,$p<0.02$) and Wilkins Echo Score (7.0+/-3.0 vs 5.8+/-2.7, $p<0.001$). This concurs with a recent study by Leon et al who showed that patients with AF have a worse short and long-term prognosis from BMV [Leon et al 1999]

Anatomic characteristics of the mitral valve were important predictors of immediate results. Most studies of BMV have found valve morphology to be the strongest independent predictor of outcome [Nishimura R et a 1990] [Palacios I et al 1995][Wilkins G et al 1988][Abascal V et al 1989][Tuzcu E]. Visualisation of calcification on X-Ray is a crude method of assessing mitral valve morphology which does not discriminate between annular, leaflet and commissural disease. However, it is relatively simple and objective and in our study fluoroscopic calcification grade was an independent predictor of outcome.

The development of cardiac ultrasound has enabled us make a more detailed assessment of mitral valve anatomy. Most centres performing BMV employ transthoracic echocardiographic scoring systems to guide patient selection, the most widely is the Wilkins Score [Wilkins G et al 1988](Appendix 1). Patients with a score of </= 8 are good candidates for BMV and have been shown to have better immediate and long-term results. In a series of 130 patients, Abascal et al [Abascal V 1989] found that 84% of those with a score of less than 8 had an optimal haemodynamic outcome (MVA >1.5 with 25% increase). However, in Abascals' series there was substantial scatter in the correlation between Echo Score and increase in area and a significant proportion (43%) of those with high echo scores of 8 or more also achieved an optimal result (Sensitivity and specificity 72% and 73%, positive and negative predictive accuracy 84% and 58% respectively). The Wilkins Score is subjective, prone to inter-observer variability and many elderly patients with severely degenerate and calcified valves are poor echo subjects. Our own analysis also showed only a modest correlation between Echo Score and increase in area. Of the four Wilkins categories, leaflet calcification was most strongly related to outcome. There was a moderate correlation between leaflet calcification detected by echo and fluoroscopic calcification grade ($r=0.69$, $p<0.01$), although only 47% of those with moderate / severe X-Ray calcification had a leaflet calcification score of >2 on echo.

Data from surgical commissurotomy series indicate a restenosis rate of 11% at a mean follow up of 6.5 years [Higgs] and 28% for a mean follow up of 11 years [Heger 1979].

With the decrease in new cases of rheumatic fever in the West, the proportion of patients presenting with recurrent mitral stenosis after surgical commissurotomy is increasing and information regarding characteristics and outcome on this group of patients is of value. Patients in our series presenting with restenosis are more likely to be female and in AF, but other clinical and valvar characteristics were not significantly different. The patients were of a similar age and valve degenerative change indicated by echo score, commissure score and fluoroscopic calcification was not increased. This probably reflects some selection bias. Anatomic studies have shown that mitral restenosis after surgical commissurotomy may be associated with recurrent fusion of the commissures, but also to rigidity of the leaflets and subvalvular apparatus without significant commissural fusion. The latter cases are unlikely to improve by repeat commissurotomy [Nakano S et al 1987] and such patients would have been referred directly to the cardiac surgeons. In agreement with other published reports [Iung B et al 1996], I showed that patients with restenosis selected for BMV obtained a similar immediate haemodynamic and symptomatic success rate without increased complications.

**4.6 Conclusions:**

In a heterogeneous population BMV was performed safely with low procedural mortality and resulted in significant haemodynamic improvement. Immediate results can be predicted from baseline clinical and anatomical variables. Male sex and sinus rhythm predict better results. As with other authors, I found valve morphology to correlate strongly with outcome. Fluoroscopic detection of the degree of calcification is a crude method for assessing valve anatomy but emerged as a strong independent predictor: to obtain >50% chance of a successful outcome, BMV should not be undertaken in those patients with moderate or severe fluoroscopic calcification. Echocardiographic assessment based on the Wilkins Score is most commonly used for the evaluation of patients referred for BMV but had poor specificity and a modest correlation with increase in valve area. Commissural morphology is not included in the Wilkins criteria

but may be of value in refining the prediction of outcome. The importance of commissural fusion and calcification will be explored in subsequent chapters.

Younger patients are more likely to have thin, pliant valves with little subvalvular change and derive the best haemodynamic results from balloon dilatation. However, there are now in the UK fewer such young patients with mitral stenosis. Of the patients in our series, 29% who were aged less than 40, including the only teenager, had immigrated to the UK from countries where rheumatic fever remains prevalent. The population we now encounter is considerably older. Elderly patients tended to be less suitable for BMV but are at significantly higher risk from cardiac surgery. Increase in valve area was less than that achieved in younger patients with pliant, non-calcified valves. However, the elderly obtained a similar degree of symptomatic improvement measured by NYHA class at 3 months, even when the initial haemodynamic response was suboptimal and complications of death or need for MVR were not increased. At least in the short term, BMV appears to offer these elderly patients useful functional improvement at low risk. Longer term follow up is required to evaluate whether this initial symptomatic benefit seen in those with a suboptimal haemodynamic result is sustained. This will be addressed in subsequent chapters.

# CHAPTER FIVE

## Long-term outcome of balloon mitral valvotomy in 300 patients

### 5.1 Background:

To justify the use of BMV as an alternative to surgery for the definitive treatment of mitral stenosis, the procedure should offer patients an acceptable period of symptomatic improvement. I have shown that BMV offers immediate symptomatic benefit in the elderly despite initial suboptimal haemodynamic results; longer-term data is required to evaluate whether this is sustained over time.

Studies of longer term outcome of BMV are starting to appear in the literature. The largest series of long term follow up was reported recently in a French series of 1024 patients, mean age 49 years followed up for a maximum 10 years, median 49 months [Iung B et al 1999]. However, most other large series report only mid-term follow up and there is limited data regarding the elderly, diverse patient subsets and patients with suboptimal immediate results

### 5.2 Aims:

To study long term (maximum 10 year) symptomatic outcome of BMV in a large heterogeneous population

To identify clinical and anatomical predictors of long term successful symptomatic outcome.

### 5.3 Patients and Methods:

Longer-term symptomatic follow up data was available for the first 300 patients out of the total 405 undergoing BMV by a single primary operator at the Western General Hospital, Edinburgh. Baseline characteristics in the 300 patients are shown in Table 11. Baseline characteristics for the 405 are similar and have been discussed in chapter 3.

Follow up of the 300 patients ranged from 1 to 10 years (mean 2.4 +/- 2.3 years) and was 97% complete (8 patients lost to follow up).

**Table 11 Baseline characteristics of 300 patients**

| | |
|---|---|
| Age (years) | 59.9+/-12.8 |
| Female | 78% |
| AF | 73% |
| History of rheumatic fever | 40% |
| NYHA class | 3.0 +/- 0.7 |
| Pre-area (cmsq) | 0.91+/-0.3 |
| Echo Score | 6.79+/-3.0 |
| Previous valvotomy | 23% |
| Parsonnet Score | 15+/- 8.8 |
| Xray calcification 0 | 54% |
| 1 | 19% |
| 2 | 10% |
| 3 | 18% |

## 5.4 Results

Univariate and multivariate cox regression analysis of factors predicting long term symptomatic outcome are shown at the end of the results text in tables 12 and 13 respectively. Kaplein Meir 10 year survival curves are also shown in Figures 12-17 where cumulative survival is defined as the proportion of patients alive, without MVR or redo valvotomy who remain improved by at least +1 NYHA class.

At 1,3,5 and 7 years, survival without MVR/repeat BMV was achieved in 70%, 60%, 49% and 42% respectively. This criteria + sustained symptomatic improvement was achieved in 61%, 52%, 42% and 33% respectively (Figure 12). Median survival without MVR or repeat BMV and improved symptoms was 4.0 +/- 0.6 years.

In our 300 patients, multivariate analysis showed five variables to be independent predictors of long term outcome after BMV: (1) post- valve area, (2) Parsonnet Score, (3) Wilkins Echo Score, (4) LV impairment and (5) MR post-BMV.

The strongest independent predictor of long term symptomatic outcome from BMV was initial haemodynamic success indicated by post- valve area. Fifty seven percent achieved an immediate successful result (MVA>1.5, no severe MR). Of these patients, 12.5% either died or required MVR at 1 year compared with 29% of those with a suboptimal initial result. Symptomatic success at five years was seen in 54% of those with a successful immediate outcome compared with only 27% of those with initial unsuccessful outcome (figure 13). Median +/- SE event free survival with symptomatic improvement was 7.0 +/- 1.1 years vs only 1.0 +/- 0.48 years for those with a successful and usuccessful immediate result, respectively.

The Parsonnet Score had an important affect on long term outcome (Figure 14). It was a significant independent predictor in multivariate analysis and was the strongest predictive factor in the over 70s age group.

Patients with more severe valvular degenerative disease indicated by the Wilkins Echo Score had poorer long term outcome with early deterioration in symptoms. Sustained

symptomatic improvement at 5 years was achieved in 49% of those with a baseline Wilkins Score of <8. Of those patients with Wilkins Scores of >8, one third had either died or been referred for MVR at a year and only 18.5% remained symptomatically improved at 5 years (Figure 16).

The development of more than mild mitral regurgitation on cine ventriculography post-dilatation resulted in an adverse long term outcome which appears striking on the survival curves shown in figure 17. Seventeen patients (5.7%) developed moderate or severe MR immediately after BMV. In most cases the MR was well tolerated at the time of valvotomy. However, at one year follow up, 10 of these patients had required MVR and another 4 had died (82% death or MVR). Of those without significant MR after BMV, only 16% had either died or required MVR at one year.

When the Parsonnet Score is removed from the multivariate model, age, X-Ray calcification and previous valvotomy emerge as independent predictors (Table 13). In the over 70 age group, previous valvotomy and X-Ray calcification were the strongest independent predictors of adverse outcome. Patients with a previous valvotomy had similar age, valve area and valve calcification compared to the others but were more likely to be female and in AF.

**Table 12. Long term symptomatic outcome in 300 patients: Univariate analysis of predictors**

| Variable | Score | P value |
|---|---|---|
| Parsonnet Score | 32.6 | <0.0001 |
| Post Area | 25.8 | <0.0001 |
| X Ray Calcification | 24.8 | <0.0001 |
| Wilkins Echo Score | 24.1 | <0.0001 |
| Age | 23.7 | <0.0001 |
| Operable | 15 | <0.001 |
| Post Gradient | 15 | <0.001 |
| Pre MR | 14.3 | <0.001 |
| LV impairment | 11.9 | <0.001 |
| NYHA class | 11.9 | <0.001 |
| CAD | 10.5 | <0.001 |
| MR post | 9.5 | <0.01 |
| Previous BMV | 6.3 | <0.01 |
| Post COP | 6.3 | <0.05 |
| Pre COP | 4.9 | <0.05 |
| Pre RV systolic Pressure | 4.9 | <0.05 |
| AF | 4.0 | <0.05 |

**Table 13. Long-term symptomatic outcome in 300 patients: Multivariate analysis of predictors with relative risks of adverse outcome (no improvement in symptoms or death, redo BMV or MVR)**

| **Parsonnet Score Excluded** | Relative risk | P value |
|---|---|---|
| Post-Area ($cm^2$) | 0.36 | <0.001 |
| X Ray Calcification (0-3) | 1.25 | 0.005 |
| Age (years) | 1.02 | 0.006 |
| MR-Post BMV (0-3) | 1.43 | 0.007 |
| LV impairment (0-3) | 1.61 | 0.021 |
| Previous Valvotomy (Y/N) | 1.44 | 0.040 |

| **Parsonnet Score included** | Relative risk | P value |
|---|---|---|
| Post-Area ($cm^2$) | 0.35 | <0.001 |
| Parsonnet Score | 1.04 | <0.001 |
| Echo Score (0-16) | 1.09 | 0.002 |
| LV Impairment (0-3) | 1.79 | 0.005 |
| Post-mitral regurgitation (0-3) | 1.35 | 0.020 |

**Figure 12 Long term success (survival without MVR or redo BMV and improved by at least +1 NYHA class) in 300 patients**

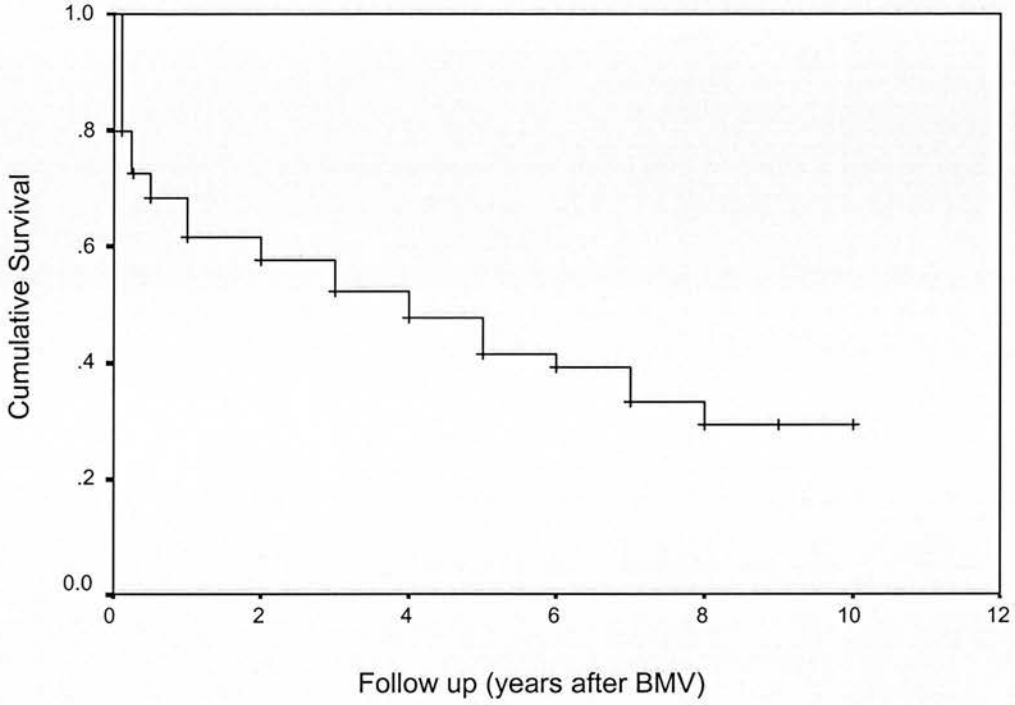



**Figure 13. Long term success: relation with immediate haemodynamic result.**

Successful immediate haemodynamic result = Final MVA >1.5cm$^2$, no severe MR

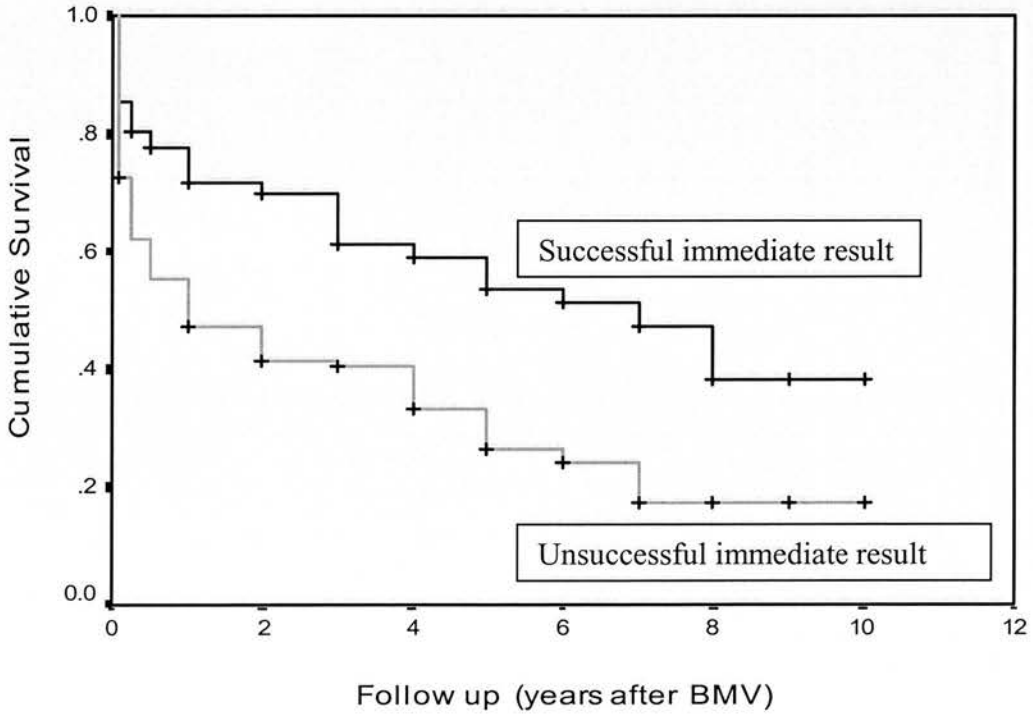


**Figure 14. Long term success: Relation with Parsonnet Score**

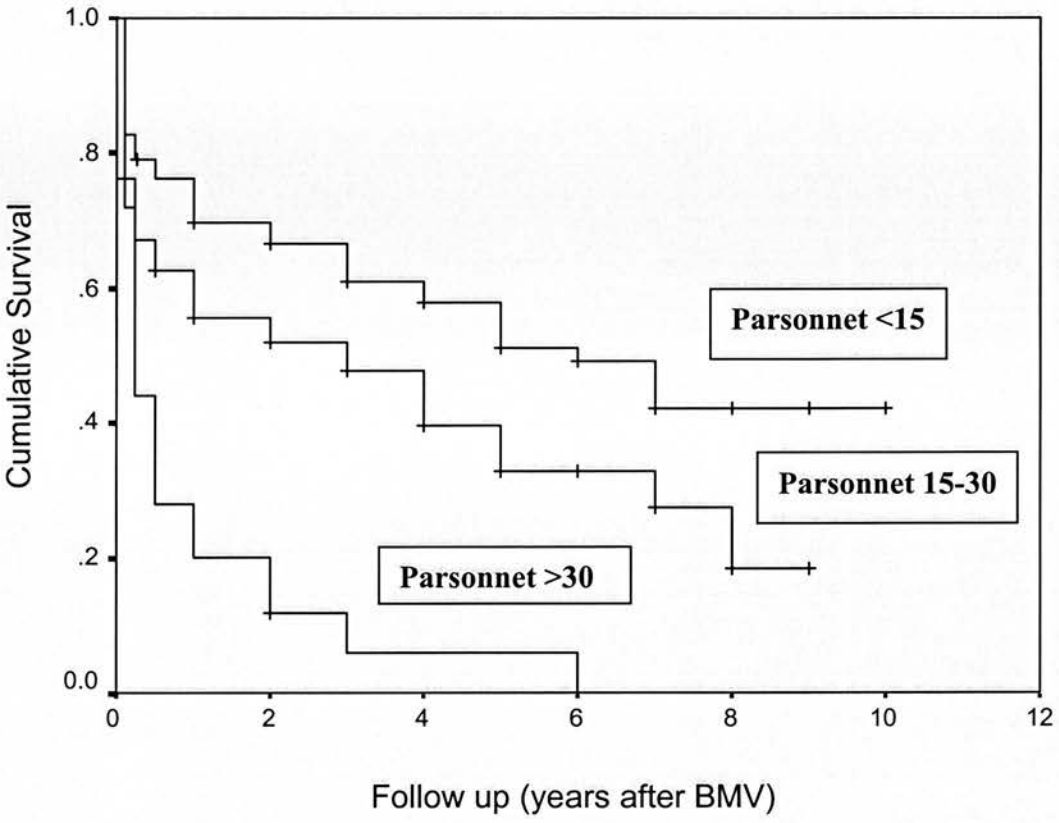


**Figure 15. Long term success: relation with age**

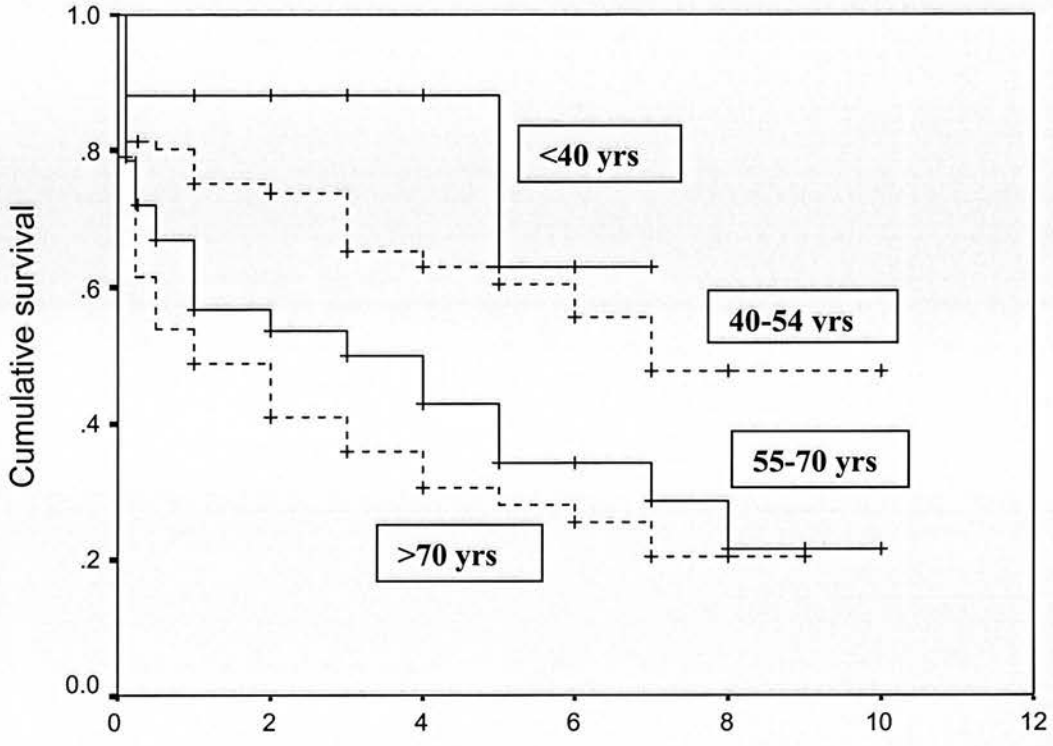


**Figure 16. Long term success: relation to Wilkins Score**

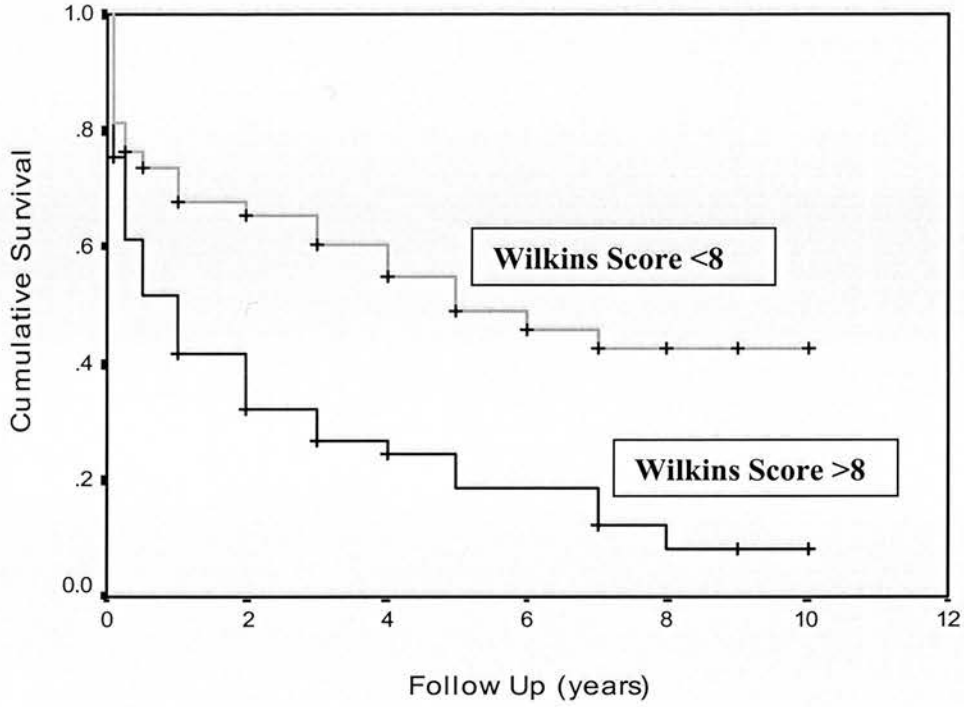
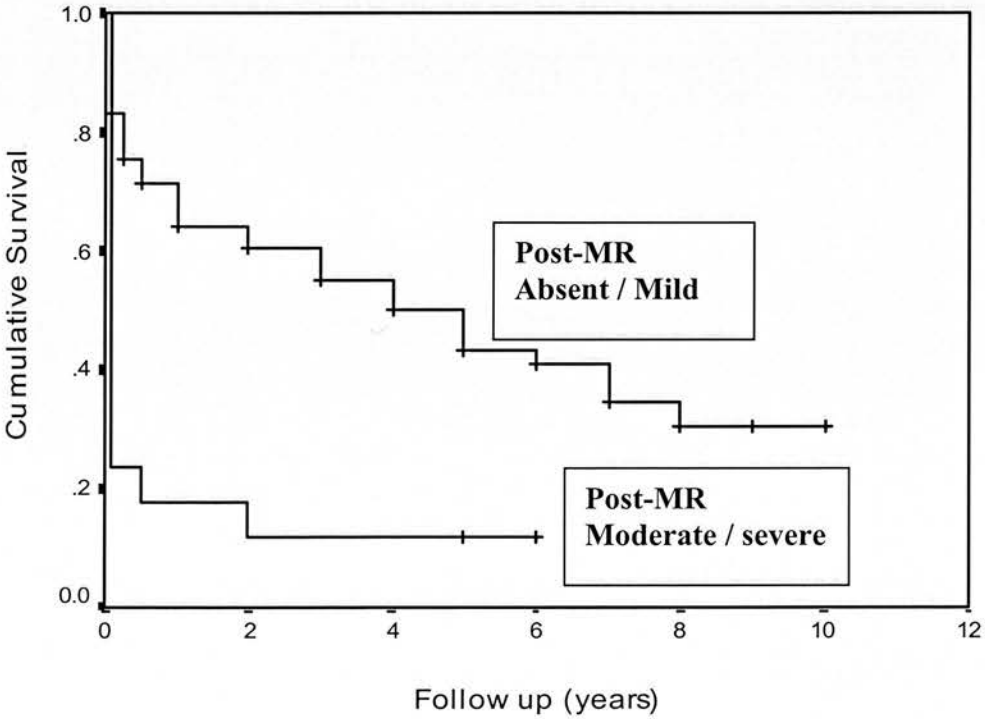



**Figure17.**

**Long term success: relation with development of MR post BMV**



**Discussion**

I report long term (maximum 10 year) outcome from BMV in 300 patients, mean age 59.9 years. This is the largest series of long term follow up in such an elderly population. Symptomatic success (alive, no MVR, +1 NYHA class) was achieved at 1,3 5 and 7 years by 61%, 52%, 42% and 33%. Poor functional outcome could be predicted by baseline anatomical and clinical patient characteristics (Parsonnet Score, advanced age, Echo Score, X-Ray calcification, LV impairment, MR, previous valvotomy). The strongest independent predictor of long term outcome was the quality of the immediate result, indicated by valve area post-BMV.

The largest study to date of long term outcome was conducted in France by Iung et al. They followed up 1024 patients for up to 10 years (median duration 4 years). Patients in this and other studies of long term outcome from BMV were younger than our UK series. In the study by Iung, patients were on average 11 years younger (mean age 49 years), less likely to have AF (40% compared with 73%) and had less severe mitral stenosis (mean MVA 1.1 compared with 0.91 cmsq). Direct comparisons with the results of our study therefore cannot be reliably made but the general trends and predictors of success are similar to our findings. Early experience from surgical commissurotomy has confirmed that good immediate results from BMV lead to sustained symptomatic improvement. Patients with a suboptimal increase in valve area or severe mitral regurgitation usually have a poor prognosis and require surgery in the months following BMV. Iung et al found that 84% of patients with poor immediate results experienced >1 cardiovascular event and the majority underwent MVR, compared with only 19% of those with good immediate results. Patients who did not undergo surgery generally had contraindications to surgery, and most of them died of cardiovascular causes or became rapidly symptomatic. Iung and colleagues showed that if BMV is initially successful survival rates are excellent, the need for subsequent surgery is infrequent, and functional improvement occurs in the majority of cases. When functional deterioration occurs in

these patients it is late and mainly related to mitral restenosis which affects 40% of patients after seven years [Hernandez R et al 1999]

The preceding chapter indicated that older patients were less likely to obtain an optimal immediate haemodynamic result from BMV. Despite this, significant symptomatic improvement was seen at 3 months. However, I have shown that this is usually short-lived and such patients suffer rapid deterioration in functional state. Age has been identified as a strong predictor of late results in series of surgical [Hickey MSJ 1991] and balloon commissurotomy [Palacios IF 1995].

The Parsonnet Score was a significant independent predictor of long term outcome. This scoring system includes an assessment of age, RV systolic pressure and comorbidity, each of which has an important impact on outcome. Although this score is used widely for risk stratification of patients undergoing cardiac surgery, it has not previously been evaluated in patients undergoing BMV. The precise cause of deterioration was not recorded in our study, many cases may have been due to associated comorbidity which would be reflected in the Parsonnet Score.

Assessment of valve morphology was a useful method for predicting long term outcome. Echo assessment based on the Wilkins Score was an independent predictor in all 300 patients and in the over 70s subgroup. With the Parsonnet Score excluded, X-Ray calcification replaced the Wilkins Score as an independent predictor. Most reported studies of mid and long term outcome after BMV have shown mitral valve anatomy assessed by various echocardiographic scoring systems and fluoroscopy to have an important impact on prognosis and a number have found this to be the strongest independent predictor of outcome [Pavlides et al 1997][Meneveau N et al 1998][Abascal V et al 1989][Cohen et al 1992]. Meneveau followed up 532 patients and reported event free survival at 7.5 years to be as high as 70% in those with favourable anatomy, falling to 16% in those with the most severe degenerative change. In their study, valve anatomy was scored according to the degree of subvalvular thickening and fluoroscopic calcification. Cohen and Pavlides used the more widely accepted Wilkins Echo Score to grade valve deformity and found this to be the strongest independent predictor of event

free survival. A higher Echo Score has been associated with more rapid progression of mitral stenosis in medically treated patients [Gordon S et al 1992]. Moreover, mitral valve calcification and immobility that are visible during the procedure, predict adverse prognosis after surgical commissurotomy.

The development of moderate or severe mitral regurgitation on fluoroscopy post-BMV conferred a dreadful prognosis. In our 300 patients, 5.7% developed grade 2 or 3 MR after BMV. Although in most cases this was well tolerated immediately after the procedure, within one year 82% of these had either died or undergone MVR. Iung and colleagues also found that a significant increase in MR resulted in adverse short and long term outcome and early MVR should be considered in such patients. Mitral regurgitation post-BMV could not be predicted from baseline factors (Chapter 4), although those with more than mild MR prior to inflation were obviously likely to have significant MR post-procedure and should be considered for MVR at the outset.

Previous surgical valvotomy predicted a worse long term outcome, despite these patients achieving a similar result. At 1 year, 19 out of 69 (27.5%) of those with a previous valvotomy had died or received a MVR, compared with 38 out of 222 (17%) of those without a previous valvotomy ($P<0.01$). There was no difference in the age, or valve morphology of the two groups, it is possible that previous valvotomy confers a more rapid rate of restenosis. This differs to the findings of Iung et al who showed that after a good immediate result, over 50% of such patients remained improved at 8 years, enabling reoperation to be deferred. However, this series included younger patients selected on the basis of bilateral commissural fusion on echocardiography.

LV impairment also emerged as an independent predictor of long term outcome in our series. Left ventricular end-diastolic pressure was a significant predictor on univariate analysis and been shown to predict survival in studies of both BMV [Cohen D et al 1992] and mitral valve replacement [Salomon N et al 1977].

## 5.6 Conclusions

Long term results of BMV in a diverse population can be predicted from baseline variables. Selection of patients referred for BMV should include a careful assessment of valve morphology, including the Wilkins echocardiographic Score and fluoroscopic calcification. The Parsonnet Score is widely used for risk stratification of patients prior to cardiac surgery, but has also been shown to be a useful and simple system for predicting long term outcome after BMV.

Those achieving a final MVA >1.5 without mitral regurgitation are much more likely to enjoy continued symptomatic benefit without the need for MVR. Where dilatation fails to improve the valve area or creates significant MR, functional deterioration is often rapid and chances of long term success are markedly reduced. The strong predictive value of the quality of the immediate results stresses the importance of carefully evaluating valve area and MR immediately after valvotomy. Valve replacement surgery should be recommended early in those failing to gain satisfactory haemodynamic improvement before further physical deterioration occurs in these elderly patients. For patients in whom unfavourable valve morphology predicts a suboptimal haemodynamic result, BMV can be expected to offer only short term palliation of symptoms. This is often the case in very elderly patients, many of whom are at high risk from cardiac surgery. No randomised study is available for older patients who have a less favourable outcome and a comparison with surgical series is difficult because of the differences in the patients involved and the fact that the surgical alternative can be not only commissurotomy but also valve replacement. The role of BMV in older patients is still debated and will be explored in the next 2 chapters.

## 5.7 Limitations

Other long term follow up series have included mainly younger patients and the results of these studies cannot be directly compared with our own. There was no randomised, case-matched control group treated by surgical commissurotomy or mitral valve replacement and it is unlikely that such studies will ever be conducted. Data on patients who subsequently underwent MVR would have been useful but continued follow up in this group was not performed. Echocardiographic follow up was not undertaken and therefore symptomatic deterioration may not solely be due to progression of mitral valve disease. NYHA class as a measure of functional success is subjective but allowed rapid assessment to be made from clinic notes and telephone contact.

# CHAPTER 6.

# Long term outcome of balloon mitral valvotomy in patients aged 70 and over.

## 6.1 Background:

In Western countries patients now presenting with severe mitral stenosis are often of advanced age as acute rheumatic fever has almost disappeared [Carrol et al 1993]. Analysis of their baseline characteristics (Chapter 3) has shown that these elderly patients have more marked valvular and subvalvular calcification and thickening unattractive for balloon dilatation. An optimal increase in valve area is less likely to be achieved, predicting a poorer longer term symptomatic outcome. Such patients would therefore normally require valve replacement. However, data from surgical series indicate that elderly patients undergoing mitral valve replacement or repair experience a higher mortality and morbidity and spend longer in hospital than younger patients [Nair et al 1992][Fremes et al 1989]. Such patients may be content with a moderate improvement in symptoms if this allows them to regain an independent although restricted lifestyle. For this type of patient, therefore, percutaneous balloon valvotomy might still represent a useful palliative treatment with lower procedural risk. As mitral balloon valvotomy carries some risk to the patient and has an economic cost it would be justified only if significant symptomatic improvement continued for a reasonable length of time. I report our experience of mitral balloon valvotomy in patients aged 70 years and over, who have been followed for one to 10 years. This study is unique in that I compared outcomes in those patients judged unfit for surgery in whom BMV is the only therapeutic option and therefore the decision to offer BMV is relatively straightforward, and those patients judged to be fit for surgery in whom the role of BMV as an alternative to mitral valve replacement remains unclear.

**6.2 Aims**:

1. To assess the immediate haemodynamic improvement and long term symptomatic benefit of BMV in 80 patients aged 70 and over

2. To compare baseline characteristics and results of BMV in patients judged suitable and unsuitable for surgery

**6.3 Patients and Methods:**

Of 300 patients who had a mitral balloon valvotomy between 1986 and 1996, 80 (27%) were aged 70 years or over. The mean age of these 80 patients was 75.2 $\pm$ 4.2 years (range 70-87:), 20 were octogenarians. There was a history of rheumatic fever or chorea in 33 (41%). A previous surgical valvotomy had been carried out in 16 (20%) at a mean of 25.3 $\pm$ 7.5 years earlier (range 12-40). Patients had been referred from hospitals throughout Scotland. All were UK-born. In an additional 4 patients balloon valvotomy could not be completed, as described below.

In this age group the clinical status of the patients varied greatly. They ranged from the fit elderly to those who were moribund. Fifty five (69%) of these 80 patients were judged unsuitable for cardiac surgery by a cardiac surgeon or referring cardiologist. The principal reason for unsuitability for surgical treatment was additional cardiac disease in 5 (severe left ventricular impairment and/or ungraftable coronary disease), pulmonary disease in 12 and marked frailty in 8. Thirty patients had medical problems which singly or in combination had resulted in the patient being considered unsuitable for surgery. The medical problems were renal impairment, chronic neurological disability, co-existent cancer, severe arthritis, severe obesity, diabetes, pulmonary or cardiac disease and moderate frailty. The mean number of additional medical problems in this group was 3.0 (range 1-7). Twenty five of the 80 patients had been considered as acceptable for surgery but had on echocardiography a mitral valve judged appropriate for treatment by balloon commissurotomy. The characteristics of the patients in these two groups is given in Table 14. Parsonnet Score, a prediction of mortality in the perioperative period, was calculated for each patient

**Table 14**

**Characteristics of 80 patients aged 70 and over undergoing mitral balloon valvotomy and judged as unsuitable or suitable for cardiac surgery.**

| | Unsuitable for surgery | Suitable for surgery |
|---|---|---|
| Patients | 55 | 25 |
| Female | 47 (86%) | 22 (88%) |
| Mean age (years) | 75.9 ± 4.4 | 73.6 ± 3.0 |
| Sinus rhythm | 5 (9%) | 4 (16%) |
| Mitral reflux | 27 (49%) | 10 (40%) |
| Aortic valve disease | 16 (29%) | 5 (20%) |
| LV impairment | 12 (22%) | 3 (12%) |
| Coronary artery disease | 29 (53%) | 5 (20%) |
| RV systolic pressure (range - mmHg) | 62 ± 24 | 47 ± 15 |
| | | |
| Symptom Class I | 0 (0%) | 0 (0%) |
| II | 1 (2%) | 4 (16%) |
| III | 26 (47%) | 14 (56%) |
| IV | 28 (51%) | 7 (28%) |
| | | |
| Mitral valve calcification: | | |
| None | 14 (25%) | 12 (48%) |
| Mild | 14 (25%) | 6 (24%) |
| Moderate | 7 (13%) | 5 (20%) |
| Severe | 20 (36%) | 2 (8%) |
| | | |
| Echo Score | 8.3 ± 3.2 | 7.4 ± 2.7 |
| Parsonnet Score | 27.3 ± 8.7 | 19.4 ± 6.0 |
| (range) | (10-45) | (13-36) |

### 6.31 Echocardiography

Transthoracic echocardiography was carried out prior to balloon valvotomy as described [section 2.4] and leaflet and subvalvar anatomy scored using Wilkins Echo Score (Appendix 1). Echo scoring was by consensus of two observers and was done prospectively in 59 patients and retrospectively from video recordings in the first 21 patients. The latter 53 (66%) patients also had a transoesophageal echo (TOE) study immediately prior to the planned procedure to exclude left atrial thrombus. In 9 (17%) of these patients left atrial thrombus was detected. The thrombus was within the auricular appendage in 5 and was a smooth laminar wall thrombus in 2. These 7 patients proceeded to same day mitral balloon valvotomy. In 2 patients thrombus protruding into the left cavity was found and both had a further 3 month period of intensified anticoagulation before undergoing balloon valvotomy. In 1 of these 2 patients the thrombus had disappeared at repeat TOE and in the other it had regressed and appeared organised. In 1 additional patient thrombus was situated at the interatrial septum; it persisted after intensive anticoagulation and she was referred for surgery. All of the patients found to have left atrial thrombus had been on warfarin therapy; 9 of the 10 were in atrial fibrillation.

### 6.32 Balloon mitral valvotomy

BMV was performed as previously described (section 2.3). In an additional 4 patients aged over 70, completed balloon dilatation at the mitral valve was not achieved. In 3 of the first 16 patients the cylindrical balloons then used could not be made to cross either the atrial septum or the mitral orifice. In one patient hemiplegia developed before Inoue balloon dilatation was complete.

### 6.33 Follow up

Symptom status (New York Heart Association (NYHA) Symptom Class) after valvotomy was established by clinic visit or telephone contact. Details of valve replacement and deaths were obtained from general practitioners and referring

physicians and Health Board mortality records. Follow up was from 1 to 10 years (mean+/-SE: 3.14 +/- 0.42 years) and was 100% complete.

## 6.4. RESULTS

Percutaneous mitral balloon dilatation was well tolerated, even in the critically ill patients, and no patient died or developed a sustained major arrhythmia, pulmonary oedema, or shock during the procedure or required a vascular repair procedure.

### 6.41 Haemodynamic change

The haemodynamic findings before and after balloon dilatation are given in Table 15. Overall the mean transmitral gradient was reduced by 52%, cardiac output rose by 27% and valve area increased by 89%. Post-dilatation valve areas greater than 1.50 sq cm and 1.20 sq cm were achieved in 40% and 67% of those unsuitable for surgery and in 60% and 80% of those suitable for surgery. A successful haemodynamic result (MVA>1.5, no MR) was achieved in 40% and 58% of those judged inoperable and operable respectively, although this difference was not significant (p=NS). In the inoperable group, patients with an Echo Score <8 were more likely to achieve haemodynamic success ($p<0.05$), in those judged to be operable echo assessment of valve morphology did not predict outcome. The increase in valve area in the 80 patients showed a significant but weak correlation with Echo Score ($r = -0.22$, $p <0.05$)(Figure 18). Other predictors of immediate outcome included pre-area, pre-cardiac output (both $P<0.001$) and X Ray calcification grade ($P<0.05$). On multiple linear regression analysis only pre-area and age were independent predictors of immediate success. Haemodynamic change was similar in the four co-morbidity subgroups.

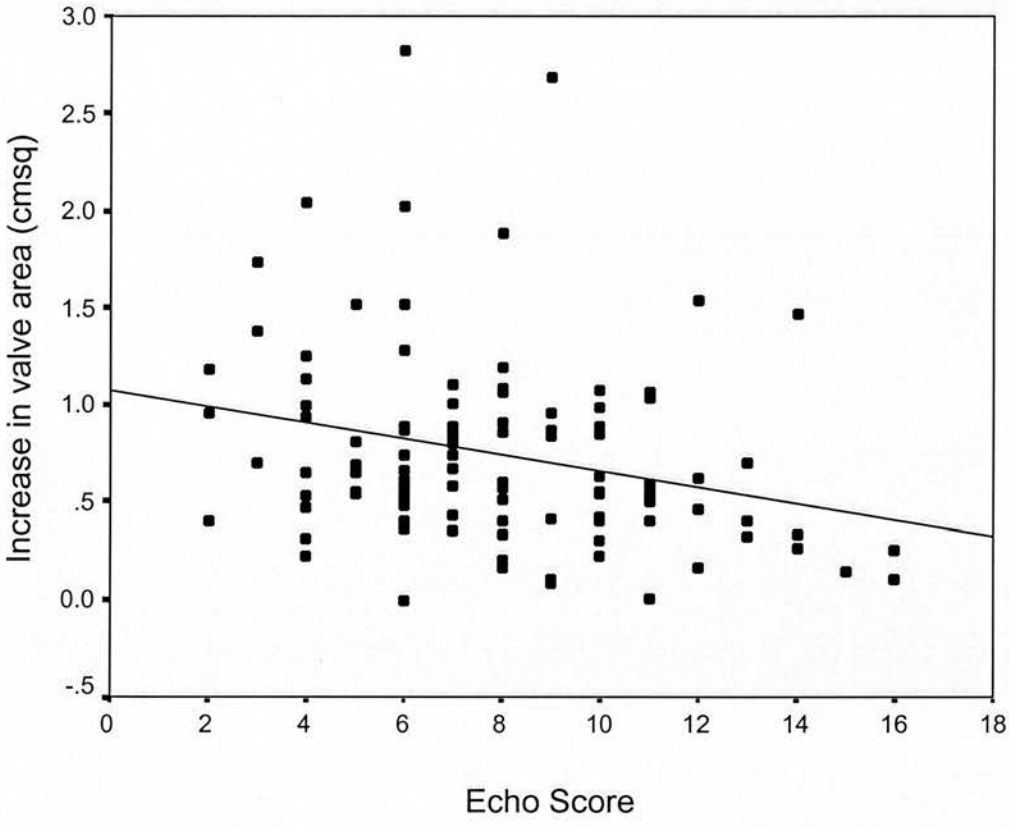
**Table 15. Haemodynamic findings before and after mitral balloon valvotomy**

**ES = Echo Score, MVA = mitral valve area  All haemodynamic changes statistically significant**

| Patients | Transmitral gradient (mmHg) | | Cardiac output (L/min) | | MVA ($cm^2$) | | Final MVA >1.5 (%) | Final MVA > 1.2 (%) |
|---|---|---|---|---|---|---|---|---|
| | pre | post | pre | post | Pre | post | | |
| All (n=80) | 11.6 | 5.6 | 3.26 | 4.15 | 0.84 | 1.59 | 46% | 71% |
| Unsuitable for surgery (n=55) | 11.9 | 5.7 | 3.26 | 4.27 | 0.81 | 1.58 | 40%<br>28% when ES>8<br>50% when ES 8 | 67%<br>44% when ES>8<br>87% when ES 8 |
| Suitable for surgery (n=25) | 11 | 5.3 | 3.27 | 3.88 | 0.89 | 1.61 | 60%<br>50% when ES>8<br>63% when ES 8 | 80%<br>67% when ES>8<br>84% when ES 8 |

**Figure 18 Correlation between echo score and increase in valve area after mitral balloon dilatation**

r= 0.22, p<0.05



### 6.42 Complications

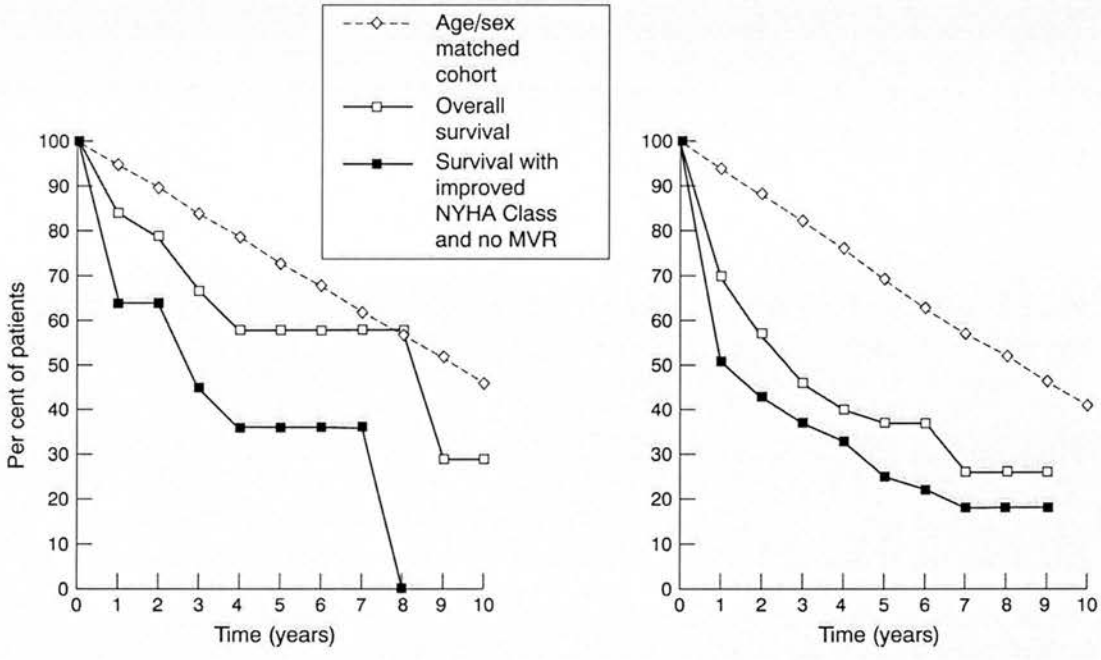
Sixteen patients (20%) developed an increase in mitral reflux after dilatation. However immediately after final dilatation reflux became mild in 11, moderate in 5 and severe in none. No patient required emergency valve replacement. In 14 patients (18%) oxygen saturation measurement detected a left to right shunt from atrial septal puncture of greater than 1.2 to 1 (mean 1.50 $\pm$ 0.39, range 1.2-2.7). One patient, treated by the double cylindrical balloon method, developed marked atrial shunting (2.7:1) and later required surgical repair of the atrial septum at the time of valve replacement. Three of the 80 patients showed evidence of systemic embolism. One patient who did not have TOE prior to balloon valvotomy, had a coronary embolus with subsequent mild LV impairment. One patient, in whom TOE showed no left atrial thrombus, had transient foot ischaemia. A patient with laminar thrombus at TOE had a transient diplopia. An additional patient, in whom mitral balloon dilatation was not completed, had protuberant left atrial thrombus which was erroneously thought to have become organised and adherent at repeat TOE after intensive anticoagulant and developed a severe hemiplegia, giving a total embolism rate of 5%. A small (1 cm) asymptomatic haemopericardium was detected on post-valvotomy echocardiography in 1 patient. A total of 2 (2.5%) of the patients therefore developed a severe persistent complication.

### 6.43 10 year symptomatic outcome

The Kaplan-Meier survival curves for patients suitable and unsuitable for surgery are shown in Figure 19 and are compared to those of age and sex matched cohorts. In such elderly patients one test of benefit is whether the patient is alive, has not undergone or been referred for valve replacement and remains improved by at least 1 NYHA symptom class. Figure 19 also shows the survival curves of those achieving this criterion.

**Figure 19**

**Survival and clinical status following BMV in patients suitable (left panel) or unsuitable (right panel) for surgery, and age and sex matched cohorts**




Of the 55 patients judged unsuitable for surgery this criterion was achieved at 1 year by just over half - 28 (51%), at 3 years by 37%, at 5 years by 25% and at 7 years by 18%. In these 55 patients initially judged unacceptable for surgery, 5 who did not improve with balloon valvotomy and remained very severely disabled were subsequently reconsidered by the cardiac surgeons and accepted for operation. However, operative mortality was 40% and only 1 patient had an improvement in symptoms, confirming the poor surgical outlook for this type of patient. In the 25 cases considered suitable for surgery the criterion was reached at 1 year by 64% and at 3, 5 and 7 years by 45%, 36% and 36% respectively. After balloon valvotomy 6 of these 25 patients had valve replacement: operative mortality was 17% and all of the survivors obtained symptomatic

benefit. Symptom class before balloon valvotomy and at 1-2 months, 1, 3, 5 and 7 years after are given in Table 16. In both groups there was a progressive loss of symptomatic benefit in survivors but improvement was maintained for several years.

**Table 16 Symptom status of patients suitable and unsuitable for surgery before balloon mitral valvotomy (BMV) and at various times afterwards**

| | | *After BMV* | | | | |
|---|---|---|---|---|---|---|
| *NYHA symptom class* | *Before BMV* | *1-2 months* | *1 year* | *3 years* | *5 years* | *7 years* |
| *Patients suitable for surgery* | | | | | | |
| I | 0 | 20 | 28 | 19 | 22 | 20 |
| II | 16 | 52 | 28 | 19 | 0 | 0 |
| III | 56 | 24 | 16 | 12 | 11 | 20 |
| IV | 4 | 4 | 0 | 0 | 0 | 0 |
| MVR | - | 0 | 12 | 19 | 22 | 20 |
| Died | - | 0 | 16 | 31 | 45 | 40 |
| (n) | (25) | (25) | (25) | (16) | (9) | (5) |
| *Patients unsuitable for surgery* | | | | | | |
| I | 0 | 15 | 15 | 9 | 3 | 0 |
| II | 2 | 49 | 33 | 21 | 16 | 10 |
| III | 49 | 25 | 9 | 14 | 16 | 16 |
| IV | 49 | 11 | 7 | 2 | 0 | 0 |
| MVR | - | 0 | 5 | 0 | 0 | 0 |
| Died | - | 0 | 31 | 54 | 65 | 74 |
| (n) | (55) | (55) | (55) | (43) | (31) | (19) |

Values are percentage or (number).

MVR, mitral valve replacement; NYHA, New York Heart Association.

Predictors of 10 year symptomatic outcome (Cox Regression) for the whole group of 80 patients included Parsonnet Score, Wilkins Echo Score and LV impairment at baseline. With the Parsonnet Score removed from the model, independent predictors of outcome are LV impairment, RV systolic pressure at baseline and age. Considering only the group of 25 patients judged operable, none of the baseline factors were predictive of long term success in either univariate or multivariate analysis.

**Subgroup of twenty octogenarians:**

20 octogenarians underwent BMV and short term data were recorded. In 15 of the 20 patients MVA increased by more than 50% compared with baseline. Eight patients obtained a final MVA>1.5 and 16 patients obtained a final MVA >1,2 cmsq.

One month following discharge, all patients were alive and none had undergone mitral valve replacement. Improvement by at least 1 NYHA class was seen at 1 month in 15 of the 20 patients with 12 patients in NYHA class I or II. There was no significant correlation between baseline variables and success at one month.

Sixteen patients were followed up for 1 year: 8 of these were still alive of whom 7 remained improved by 1 NYHA class. Two patients had undergone mitral valve replacement, one because of no symptomatic improvement and one for later development of mitral reflux: both died during surgery. An additional 3 patients died from congestive cardiac failure, 2 from bronchopneumonia and one death occurred as the result of an accident.

Favourable valve morphology was a powerful predictor of successful outcome at 1 year. Of the seven patients alive and symptomatically improved, all had a Wilkins Echo Score of less than eight ($P<0.01$) and only one had more than mild fluoroscopic mitral calcification.

## 6.5 Discussion

Percutaneous mitral balloon valvotomy was well tolerated in this group of elderly, often frail and sometimes very ill patients and produced haemodynamic improvement. The low rate of complications was similar to that found in younger patients [Dean, Circulation 1994] although the final mitral valve area was smaller than in young patients with pliable valves. The procedure would be justified however only if it appeared to offer a better outcome than continued medical therapy or surgical treatment.

In 94% of the patients there was very severe symptomatic limitation (NYHA III and IV) despite intensive medical treatment. In these patients medical therapy had been maintained longer than would be usual for younger, more active patients. Continued medical treatment was not an effective option for these patients: some were bed-bound and for many others their cardiac symptoms threatened their independent lifestyle.

Mitral valve replacement in the elderly has a much higher mortality and poorer outcome than in younger patients. Nicolaou and Kinsley [Nicolaou 1984] reported a 23% 30 day mortality in 35 patients aged over 70 undergoing mitral valve replacement. Post operative complications occurred in 57% and mean hospital stay was 16 days. Nair found a 27% peri-operative mortality in 26 patients aged over 70, compared to 12% in younger patients: at 5 years after mitral valve replacement 54% of their elderly patients had died [Nair et al 1992]. Edmunds [Edmunds et al 1988] reported a 90-day mortality of 29% in octogenarians undergoing valve replacement. In a large series of 504 patients aged over 70 who had mitral valve replacement (35% with concomitant coronary bypass grafts and 38% with an additional valve replacement) between 1976 and 1996 Grossi [Grossi et al 1998] reported a hospital mortality of 17%: for mitral valve replacement alone mortality was 13%. Even after surviving mitral valve replacement, patients aged over 70 have about 50% mortality at 4-5 years after operation [Edmunds 1998] and the majority remain symptomatic.

Fifty five of our 80 elderly patients were considered to be unsuitable for surgical treatment because of their frailty or additional medical problems. Their Parsonnet Score predicted a peri-operative mortality of 27%. Many of these 55 patients had degenerative changes at the mitral valve and there was a high mean Echo Score of 8.3: mitral balloon dilatation had been undertaken even when the valve anatomy was unattractive for commissurotomy. In these circumstances balloon valvotomy might still be a useful palliative procedure for the inoperable patient if even a moderate improvement in symptoms was achieved. In this group, 51% were alive and improved by at least one symptom class at one year after the procedure. This benefit decreased with time but lasted a reasonable period, given the age and medical condition of the patients. Iung et al[Iung, EHJ 1995] achieved a mitral valve area greater than 1.5 $cm^2$ in 66% of their 75 patients aged over 70 undergoing mitral balloon valvotomy: 4 year survival was 59%.

Our 25 elderly patients who were suitable for surgery underwent balloon valvotomy because their valve anatomy appeared favourable for commissurotomy or because of the patients reluctance to undergo operation: only 6 of the 25 patients had an Echo Score greater than 8. At 1 year after balloon valvotomy 64% remained improved by at least one NYHA symptoms class, without valve replacement. Six of the 25 patients subsequently had valve replacement with a peri-operative mortality of 17%. These patients, with a mean age of 74, therefore fared moderately well after balloon valvotomy but significant symptomatic improvement was not achieved in one third at one year. In this group of patients, outcome could not be predicted from baseline anatomical or clinical variables. Ideally echocardiography would select accurately those patients who would obtain substantial haemodynamic and symptomatic improvement from balloon dilatation. I found, as have others, that the Wilkins Echo Score was an imperfect predictor of increase in valve area. There is clearly a need to improve case selection so that in those patients suitable for surgery one could identify those who would achieve adequate symptomatic improvement by balloon dilatation, while taking account of the more restricted desired lifestyle of the elderly and their higher surgical risk. Evaluation of commissural calcification has been shown to improve the prediction of outcome after

BMV [Fatkin 1993][Cannan 1997] and could refine the case selection of elderly patients. As yet the importance of commissural calcification on long term results in large numbers of patients has not been reported, this will be a focus in subsequent chapters.

Left atrial thrombus was found in 10 of the 54 patients who had TOE immediately prior to planned balloon valvotomy despite all being on Warfarin therapy. This was a higher incidence than found in younger patients. Mitral balloon dilatation was safely undertaken in those with appendicular or laminar thrombus but any thrombus protruding into the left atrial cavity should be a contraindication to balloon valvotomy.

This study included only patients referred for consideration for mitral balloon valvotomy and does not reflect the characteristics of all patients aged over 70 who have mitral stenosis. Relatively fit patients with markedly degenerate mitral valves may have been referred by their cardiologist direct for cardiac surgery. Other frail patients with severe mitral stenosis who were sufficiently controlled on medical treatment may not have been referred for balloon valvotomy.

**Conclusions**

Percutaneous balloon valvotomy can help to achieve symptomatic benefit and a return to independence for many elderly patients with mitral stenosis. In severely symptomatic patients unable to have cardiac surgery, percutaneous balloon valvotomy is virtually always worth attempting if there is any commissural fusion. In elderly patients in whom echocardiography demonstrates a valve unsuitable for BMV, only short term improvement can be expected and mitral valve replacement would be the best choice for those individuals acceptable to the surgeon. However, in patients who are judged to be unfit for MVR or who decline surgery, BMV should be considered as a short-term palliative treatment. I found elderly patients gained useful short term symptomatic benefit from BMV, even after a poor result from dilatation. Although precise data on the prognosis of severe mitral stenosis in older patients is lacking, short term symptomatic improvement should be considered a beneficial outcome in such severely disabled

individuals. Such elderly patients with severe symptomatic mitral stenosis should be referred to a cardiac centre for assessment. In elderly patients who are acceptable for operation the Echo Score gives an approximate prediction of balloon valvotomy outcome but remains imperfect: transoesophageal assessment of commissure fusion and morphology may help to improve assessment and this will be discussed in a later chapter.

# CHAPTER SEVEN

## The significance of commissural calcification on outcome of mitral balloon valvotomy:

## A *transthoracic echocardiographic study*

### 7.1 Background:

Both immediate and long term success of BMV depend heavily on the underlying mitral valve morphology and this is currently assessed using the Wilkins Echo Score. Although this scoring system has been shown to correlate with outcome of valvotomy in large groups of patients its value in the prospective selection of individual patients for the procedure has been questioned due to the weakness and scatter of individual predictive correlations, and their poor negative predictive accuracy. Our own analysis showed that one third of patients with a low Wilkins Score failed to achieve a valve area of >1.5 without MR and tended to deteriorate rapidly after BMV. 78% of such patients were judged operable and would have been better served by MVR. Additionally, a third of those with a high Wilkins Score predicting an adverse outcome obtained a good initial result from BMV. In the early study by Abascal et al, 43% of patients with a score of >8 had a good outcome. In our over 70s population, patients judged fit for surgery were selected for BMV if echocardiography showed the valve anatomy to be suitable. However, 40% of this group failed to obtain a final valve area >1.5 after BMV and symptomatic benefit was sustained at 1, 3 and 5 years in only 64%, 45% and 36% respectively. In the elderly, BMV potentially offers both a definitive and palliative treatment option but echocardiographic assessment must be refined in order to improve case selection.

*In vivo* and *in vitro* studies [Reid CL 1987][Kaplan JD 1987] have confirmed that the mechanism underlying the increase in valve area associated with BMV involves the

splitting of one or both fused mitral commissures in a manner similar to surgical commissurotomy. Calcified commissures tended to resist splitting by the balloon. Therefore, assessment of commissural morphology should intuitively be an integral part of assessment of patients referred for BMV. The Wilkins Score, however, does not include commissural assessment and this is a major limitation of the scoring system.

There have been only two reports, with relatively small patient numbers, of the importance of commissural morphology on outcome of BMV. In 149 patients investigated by Cannan *et al* [Cannan 1997], the mitral commissures were assessed in the short axis parasternal view. Commissural calcification was associated with a lower survival rate and a higher incidence of mitral valve replacement after BMV. Fatkin *et al* [Fatkin 1993] studied 30 patients using a similar transthoracic approach and demonstrated that an assessment of commissural disease prior to BMV is useful for the prediction of commissural splitting and the final increase in valve area. Both showed that evaluation of commissural calcification is more useful than the Wilkins score in predicting immediate and mid-term outcome. I report the incidence and epidemiology of echocardiographic commissural calcification in our large elderly population and study its relationship with outcome.

**7.2 Aims:**

1. To evaluate the epidemiological characteristics of commissural calcification in patients undergoing BMV

2. To investigate the significance of commissural calcification detected by transthoracic echocardiography on immediate and long term outcome of mitral balloon valvotomy.

## 7.3 PATIENTS AND METHODS

### Patients

405 consecutive patients (mean age 61 +/- 12 years) undergoing BMV were studied. Invasive haemodynamic data was recorded immediately before and after BMV (Chapter 2) Long term symptomatic outcome was available for the first 300 patients, follow up ranged from 1 to 10 years, mean 2.5 +/- 2.4 years, median 2.0 years. Baseline characteristics of the patients have been described (Chapter 3, Table 4)

### Echocardiographic assessment

The mitral valve leaflet and subvalvular degenerative change was scored on the transthoracic parasternal long axis images as described by Wilkins (Appendix 1).

The mitral valve commissures were examined in the short axis parasternal view, noting areas of calcification as evidenced by bright, confluent echos. The extent of commissural calcification was quantified by grading each half commissure with such echoes as 1 (Section 2.4). The 'Commissure Calcification Grade' for the valve could range from 0 to 4. A Commissure Calcification Grade of 2 could correspond to calcification of one commissure or to calcification of half of both commissures: infact, in 96% of cases with a grade of 2, calcification was localised to one commissure. No patient had a Commissure Calcification Grade of 4.

During the 10-year period, echocardiographic assessment was by consensus of two doctors who each performed a transthoracic echocardiogram prior to the procedure in the latter 320 patients and retrospective review by TRDS from blinded video recordings in the first 85 patients.

## 7.4 RESULTS

### Echo Findings

The mean Wilkins Echo Score was 6.6 +/- 2.9 (range 2-16). Ninety two patients (23%) received a score of >8.

Commissural calcification was identified in 110 patients (27%), 14% had a Commissure Calcification Grade of 2 or more.

**Factors associated with commissural calcification**

Relationships between the degree of commissural calcification and clinical and echocardiographic variables are shown in table 17. The degree of commissural calcification correlated strongly with pre-area, increasing age, male gender, clinical status (as assessed by NYHA class and Parsonnet Score), the presence of left ventricular impairment or coronary artery disease, radiographic mitral calcification and Wilkins Echo Score. Multivariate regression analysis demonstrated that pre-area, male sex and Wilkins Score were independent predictors of commissural calcification.

**Table 17 Relationship between baseline variables and commissural calcification**

| Commissure Calcification Grade | 0 | 1 | 2 | 3 | P |
|---|---|---|---|---|---|
| Number of Patients | 296 | 53 | 53 | 4 | |
| Age (years) | 60 | 63 | 65 | 55 | <0.01 |
| Gender (M:F) | 55:241 | 14:39 | 13:40 | 3:1 | <0.05 |
| Rheumatic Fever (%) | 37 | 36 | 51 | 50 | NS |
| Atrial fibrillation (%) | 71 | 75 | 81 | 25 | NS |
| Surgical Valvotomy (%) | 22 | 19 | 23 | 25 | NS |
| NYHA | 2.9 | 3 | 3.4 | 2.7 | <0.001 |
| Parsonnet Score | 14.6 | 16.3 | 16.8 | 17 | <0.05 |
| X-Ray Cal Score | 0.59 | 0.91 | 1.81 | 2.25 | <0.01 |
| Aortic valve disease (%) | 17 | 21 | 17 | 25 | NS |
| LV Impairment (%) | 9 | 13 | 17 | 25 | <0.05 |
| Pre-Area (sqcm) | 0.97 | 0.85 | 0.75 | 0.72 | <0.01 |
| Coronary disease (%) | 18 | 32 | 30 | 0 | <0.05 |
| Wilkins Echo Score | 6 | 7.3 | 9.2 | 8.2 | <0.001 |
| Mitral regurgitation (%) | 35 | 40 | 34 | 25 | NS |

**Echocardiographic prediction of immediate haemodynamic result**

Both Wilkins Score and Commissure Calcium Grade correlated significantly with immediate outcome from BMV (Table 18).

**Table 18: Relationship between the mitral valve area before and after balloon dilation and the Echo Score and Commissure Calcification Grade. Mean (+/- SE)**

| **Echo Score** | **1-4** | **5-8** | **9-12** | **13-16** | p value ANOVA |
|---|---|---|---|---|---|
| Number of patients | 111 | 203 | 73 | 18 | |
| Valve area before dilatation ($cm^2$) | 1.10(± 0.03) | 0.9(± 0.02) | 0.79(± 0.03) | 0.66(± 0.06) | <0.0001 |
| Valve area after dilatation ($cm^2$) | 2.12(± 0.08) | 1.68(± 0.05) | 1.48(± 0.06) | 1.17(± 0.11) | <0.0001 |
| Increase in valve area ($cm^2$) | 1.0(± 0.07) | 0.78(± 0.03) | 0.70(± 0.06) | 0.51(± 0.11) | <0.02 |

| **Commissure Calcification Grade** | **0** | **1** | **2** | **3** | P value ANOVA |
|---|---|---|---|---|---|
| Number of patients | 295 | 53 | 53 | 4 | |
| Pre-valve area before dilatation ($cm^2$) | 0.97(± 0.02) | 0.85 (± 0.03) | 0.75 (± 0.03) | 0.72(± .04) | <0.001 |
| Valve area after dilatation ($cm^2$) | 1.82(± 0.04) | 1.7 (± 0.1) | 1.40 (± 0.06) | 1.21 (± 0.2) | <0.001 |
| Increase in valve area ($cm^2$) | 0.85(± 0.03) | 0.85 (± 0.08) | 0.61 (± 0.06) | 0.49 (± 0.2) | <0.05 |

The different types of degenerative mitral valve change tended to develop together. Increasing echo score, reflecting leaflet and subvalvar changes, was significantly associated with increasing commissural calcification (table 19).

**Table 19 Commissural calcification grade in each of four ranges of echo score**

| Echo Score | Commissure Calcification Grade | Number of patients |
|---|---|---|
| 1-4 | 0.1+/-0.3 | 111 |
| 5-8 | 0.5+/-0.8 | 203 |
| 9-12 | 0.6+/-0.8 | 74 |
| 13-16 | 1.4+/-1.0 | 18 |

In patients with an Echo Score ⩽ 8 ('good valves'), those with a commissure calcification grade of 2/3 achieved a significantly lower increase in valve area than those with grade 0/1 (Table 20). There was no significant difference seen in those with an Echo Score >8 ('Bad valves'). Therefore, in patients without marked degenerative disease of the leaflets or subvalvular apparatus, the Commissure Calcification Grade is of additional predictive value.

**Table 20: Effect of commissure calcification on increase in mitral valve area in patients with Echo Score ⩽ 8 and Echo Score > 8. Values are mean (SD).**

| Commissure calcification grade | Increase in valve area ($cm^2$) | Final valve area $> 1.50\ cm^2$ |
|---|---|---|
| Patients with echo scores ⩽ 8 | | |
| 0/1 | 0.90 (0.64) | 67% |
| 2/3 | 0.67 (0.47) | 46% |
| | ($p < 0.01$) | ($p < 0.05$) |
| Patients with echo scores > 8 | | |
| 0/1 | 0.69 (0.51) | 43% |
| 2/3 | 0.62 (0.45) | 19% |
| | (NS) | (NS) |

**Predictors of immediate haemodynamic outcome**

By univariate analysis, the following patient characteristics were predictive of a final valve area >1.50 sq.cm without severe mitral reflux: younger age, lower commissural calcification grade, lower Echo Score, less fluoroscopic calcification, lower Parsonnet Score (all $p<0.001$), sinus rhythm, male sex, and absence of mitral reflux (all $p<0.01$). Previous valvotomy, effective balloon dilation area/sq.m BSA, type of balloon, left

ventricular impairment and coronary disease were not significantly related to this outcome.

On multivariate analysis less fluoroscopic calcification, male sex, sinus rhythm, and lower commissure calcification grade ($p<0.01$) were independent predictors of this outcome.

**Echo Score, Commissural calcification and symptomatic improvement**

Table 21 shows the NYHA symptom class scores before mitral balloon valvotomy and at follow up 1-3 months later. In patients with an echo score of ⩽ 8, those with commissure calcification grade 0/1 had a significantly greater improvement in symptoms than those with grade 2/3. No difference was seen in those with an echo score of > 8

**Table 21. Symptom class before mitral balloon valvotomy and alive at 1-3 months follow up in patients with echo score ⩽ 8 and > 8 Values are mean (SD)**

| Commissure calcification grade | Number of patients | NYHA symptom class before balloon valvotomy | NYHA symptom class at 1-3 month follow up | Change in NYHA symptom class |
|---|---|---|---|---|
| Patients with echo score ⩽ 8 | | | | |
| 0/1 | 200 | 2.9 (0.7) | 1.6 (0.8) | 1.2 (0.7) |
| 2/3 | 27 | 3.1 (0.6) | 2.2 (0.8) | 0.9 (0.8) |
| | | (NS) | ($p < 0.01$) | ($p < 0.05$) |
| Patients with echo score > 8 | | | | |
| 0/1 | 48 | 3.4 (0.7) | 2.2 (1.0) | 1.2 (0.8) |
| 2/3 | 19 | 3.4 (0.7) | 2.2 (0.7) | 1.2 (0.8) |
| | | (NS) | (NS) | (NS) |

**Mitral reflux after final dilatation**

An increase in mitral reflux by two or more grades occurred in 4.1% of patients with commissure calcification grade 2/3 and in 2.8% of those with grade 0/1(NS).

**Predictors of long term symptomatic outcome**

Multivariate (Cox Hazard Regression) analysis of factors affecting long term functional outcome over 10 years revealed nine variables as independent predictors. In order of significance and with relative risks (RR) of adverse outcome (death, failure of symptomatic improvement, redo BMV or MVR), these were: Increase in MVA $cm^2$ (RR=0.29), Parsonnet Score (RR=1.04), Pre-mean LA gradient mmHg (RR=0.95), LVEDP mmHg (RR=1.07), Post-MR 0-3 (RR=1.46) post-cardiac output (RR=1.21), Commissure Calcification Grade 0-3 (RR=1.29), LV impairment 0-3 (RR=1.68), Pre-MR 0-3 (RR=1.42). The Wilkins Echo Score was not an independent predictor of outcome.

The impact of Commissure Calcification Grade on long term symptomatic outcome is impressive (figure 20a). Of those with a Commissure calcification grade of 0 or 1, 50% are alive and improved without MVR at 5 years, only 12% of those with commissure calcification grade 2 or 3 achieve this success. The median survival with symptomatic improvement and no referral for MVR is 5 +/-0.88 years in those with a commissure calcification grade of 0/1 compared with 0.5+/-0.32 years in those with more extensive commissural calcification.

The most favourable long term outcome was seen in patients with the combined characteristics of a 'good Wilkins Valve' (Wilkins Score $\leqslant$ 8) and a splittable commissure (Commissure calcification Grade 0/1): median survival with sustained symptomatic improvement without MVR was 7.24 years and this criterion was reached in 84%, 77%, 68% and 60% at 1,3,5 and 7 years respectively (Figure 20b)

**Figure 20a: relationship between commissural calcification grade and long term success (alive without MVR and improved NYHA class)**

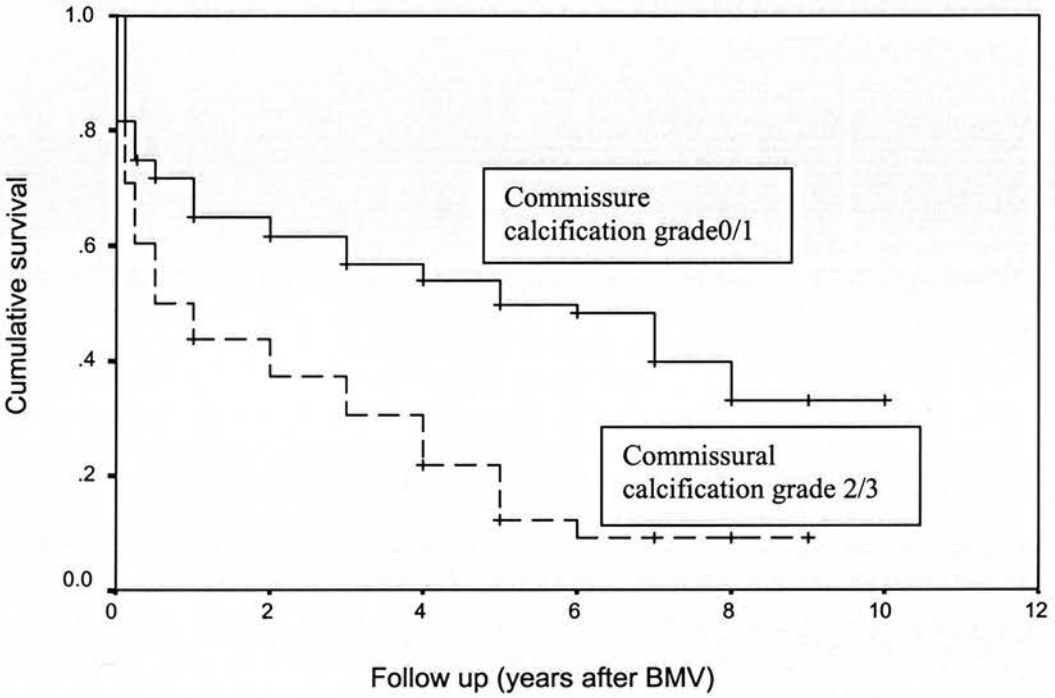
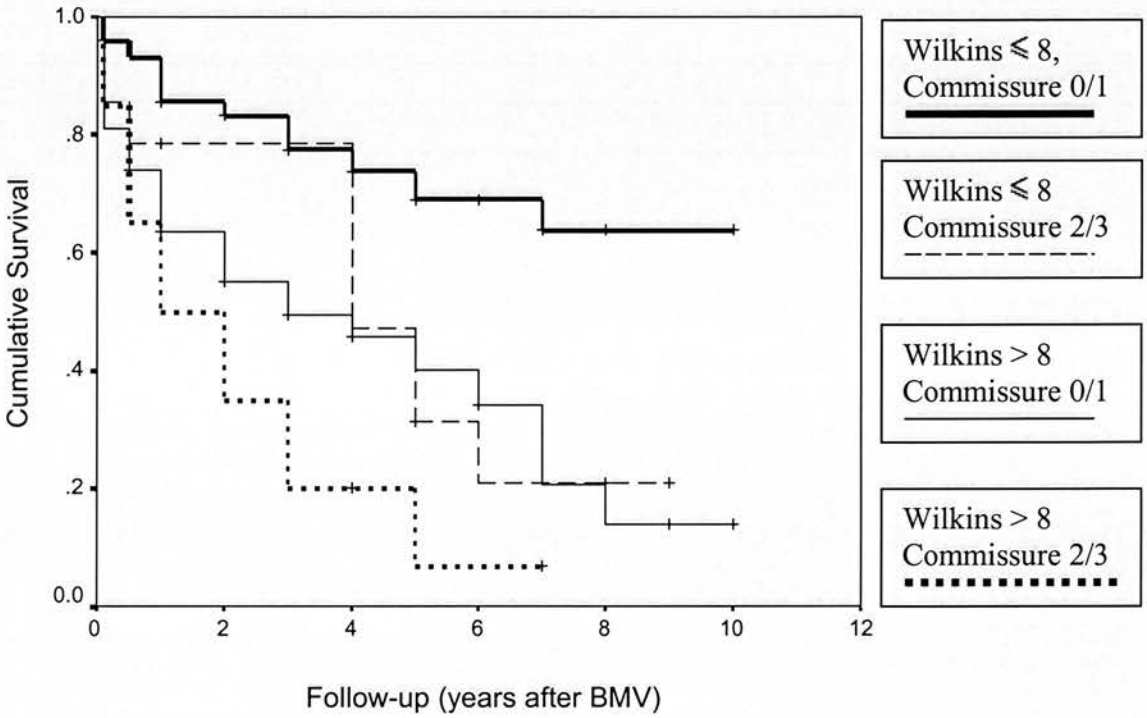


**Figure 20b. Combined Wilkins Score and commissure calcification grade: Affect on long term outcome**



## 7.5 Discussion

Percutaneous mitral balloon valvotomy has two roles: as an alternative to open or closed surgical valvotomy in patients with a mitral valve judged suitable for commissurotomy, and as a palliative procedure in patients requiring valve replacement but considered to be very high risk surgical candidates. Our series contained many elderly patients and 30% had been judged unsuitable for surgery, so there was a wide spectrum of mitral valve degenerative change.

I confirmed the relationship between the Wilkins Echo Score and haemodynamic and symptomatic status before and after mitral balloon valvotomy but the Echo Score was a weak predictor of increase in valve area for individual cases. Commissural calcification was common in this elderly population (27% of valves) and was more likely to occur with increasing age, in males and in those with more severe leaflet and subvalvular degenerative change indicated by a higher Wilkins Score. In those patients with an Echo Score of 8 or less, who are generally held to be suitable for balloon valvotomy, I found that commissural calcification had a significant influence on both the increase in mitral valve area and in symptomatic improvement. If a less than 50% probability of achieving a valve area greater than 1.50 sq.cm by balloon dilatation is taken to be a justification for valve replacement, then commissure calcification occupying the equivalent of one of the two mitral commissures would be an indication for valve replacement rather than balloon valvotomy. In patients with a low Echo Score (<8) and little or no commissural calcification, percutaneous balloon dilatation offers significant haemodynamic and symptomatic improvement which is sustained in 56% to 5 years. BMV is therefore the preferred option in this population when cardiac catheterisation facilities and transseptal puncture skills are available in view of reduced patient discomfort, short convalescence and equivalent outcome. Patients with a higher commissural calcification grade deteriorate rapidly with only 12% remaining symptomatically improved at 5 years and therefore MVR should be considered in those with acceptable surgical risk. Multivariate analysis showed that echocardiographic grading of commissural calcification was more useful than the more widely accepted Wilkins Echo Score. There has been only one

other study evaluating the impact of commissural calcification on longer term prognosis after BMV. Cannan et al [Cannan 1997] reported medium term follow up (mean 1.8 years, range 30 days to 8 years) in 149 patients undergoing BMV. Absence of commissural calcification predicted improved survival at 36 months free from the combined endpoint of death, repeat balloon valvotomy or need for MVR (86% vs 4%, $p<0.001$). Actuarial event free survival rates were superior in those without commissural calcification and Cox regression analysis showed commissural calcification to be the only independent predictor, superior to the Wilkins Score.

Fatkin et al [Fatkin 1993] also found that commissural echo-calcification predicted commissural splitting in their group of 30 patients. Cannan et al [Cannan 1997] found that in their 149 patients, commissural calcium was the only factor significantly affecting clinical outcome after mitral balloon valvotomy. In these smaller studies, the extent of commissure calcification was not quantified. Hernandez et al [Hernandez R 1999] noted that commissural calcium, identified by echocardiography, had been present in patients who developed severe mitral reflux at Inoue mitral balloon valvotomy. This could occur if resistance to commissural splitting led to leaflet tear. I found that a marked increase in mitral reflux was uncommon, although found slightly more frequently in those with marked commissural calcification (4.1% versus 2.8%). If balloon dilatation is undertaken in a patient with commissural calcification then smaller initial balloon size and a cautious progressive increase in balloon diameter should be used.

In patients with an Echo Score >8, I was not able to show a separate significant effect of commissural calcification on increase in valve area, although the same trend was present. Although such mitral valves are not ideal for a commissurotomy, percutaneous balloon dilatation may be justified if the patient is unsuitable for surgery because of comorbidity. Even limited haemodynamic improvement may give sufficient symptomatic relief to maintain an independent lifestyle [Bernard Y 1992].

Mitral valve calcification seen at fluoroscopy was also a predictor of outcome. However, fluoroscopy cannot accurately localise the calcific change and calcification can affect outcome either through leaflet rigidity or commissural resistance.

Echocardiography is preferred to localise any mitral calcification to the annulus, the body of the leaflets or the commissures. This is helpful when there is slight calcification localised at the commissure or, with generalised calcification, when splitting of commissures may give a useful palliative result.

It would be desirable to improve the echocardiographic predictability of outcome of mitral balloon valvotomy. The Echo Score is semi-quantitative and subjective. In a multi-centre registry study, the Echo Score did not show a significant link with outcome [Herrmann HC, 1992] but Post et al[Post JR 1995] found that on review of 87 patients initially judged to have an Echo Score 10, 18 were reclassified as having lower scores when judged by single-centre observers.

In this study, commissural calcification grade was assessed at transthoracic echocardiography and it was found that calcification equivalent to one commissure was associated with a less than 50% probability of achieving a good haemodynamic outcome. Transoesophageal examination of both commissural calcification and fusion may lead to further improved prediction of outcome by balloon commissurotomy, particularly in patients who are difficult to scan from the transthoracic approach.

# CHAPTER EIGHT

## Assessment of mitral valve commissural fusion and calcification:

## *Transoesophageal echocardiographic study*

### 8.1 Background

Commissural splitting is the dominant mechanism of mitral balloon valvotomy. Results of our own study and those of others [Cannan C et al 1997][Fatkin D et al 1993] have shown that the echocardiographic assessment of commissural calcification can improve the prediction of immediate and longer term outcome after BMV, adding significantly to the currently accepted Wilkins Score. These studies have used transthoracic echo. However, elderly and obese patients are sometimes difficult transthoracic subjects.

Transoesophageal echocardiography (TOE) is now performed routinely in most centres prior to BMV, primarily to exclude left atrial thrombus. In comparison with TTE, TOE offers superior resolution of the mitral valve apparatus and overcomes problems caused by anterior leaflet shadowing, thereby allowing more accurate localisation of mitral calcification. We have developed a novel TOE method which provides a systematic scan of the whole length of the mitral commissure.

### 8.2 Aims:

(1) to evaluate this new TOE technique in assessing mitral commissural fusion and calcification,

(2) to devise a Commissure Score based on TOE assessment to reflect the likelihood of commissural splitting.

(3) to determine the accuracy of this Commissure Score in predicting immediate outcome after BMV

(4) to investigate the accuracy of TTE assessment of mitral commissural morphology compared with TOE in a subset of patients.

(5) to compare the Commissure Score derived by TOE with the currently established Wilkins Score.

## 8.3 Methods

### 8.31 Patients

The series consisted of 72 patients with symptomatic mitral stenosis undergoing BMV, mean age of 61.3 years (range 38 - 89 years). The majority (83%) were female and 66% were in atrial fibrillation. Fifteen patients (21%) had presented with restenosis after a previous surgical valvotomy. In eight patients judged inoperable by the referring physician or cardiac surgeon, BMV was performed as a palliative treatment.

### 8.32 Echocardiographic study

*Transthoracic echocardiography*:

Initial MVA was derived by the Doppler pressure half time method taking the mean value of five recordings. TTE was repeated within 24 hours of BMV and at 1 month. The severity of mitral regurgitation post-BMV was assessed by colour and continuous wave Doppler ultrasound.

Final MVA was measured by either planimetry of the mitral valve orifice in the parasternal short axis view within 24 hours post-BMV, or by Doppler pressure half time at 1 month follow up. A good outcome was defined as final MVA >1.5 $cm^2$ and an increase in valve area of >25% of the baseline value in the absence of severe mitral regurgitation (MR) on echocardiography.

TTE assessment of commissural morphology was performed in the parasternal short-axis view, as described in section 2.4. Both anterolateral and posteromedial mitral commissures were individually examined for areas of confluent bright echos, taken to indicate calcification.

*Transoesophageal echocardiography*:

TOE was performed in all patients immediately prior to BMV. The mitral valve leaflets and subvalvular apparatus were examined in detail at midoesophageal and transgastric levels and mitral valve anatomy was scored according to the criteria of Wilkins *et al* [Appendix 1]. The mitral valve commissures were scanned systematically at

midoesophageal level and scored as described in Methods Section 2.5. Briefly, each commissure was assigned a score according to whether non-calcified fusion was absent (0), partial (1) or extensive (2). Calcified commissures usually resist splitting and scored 0. Both commissures were combined giving an overall 'Commissure Score' for each valve of 0-4. Higher scores reflecting more extensively fused, non calcified commissures which were therefore more likely to split, whereas a low score indicated either minimal fusion or the presence of resistant commissural calcification.

### 8.33 Interobserver variability of TOE assessment

The TOE images of 30 patients (60 commissures) were retrospectively reviewed by 2 independent observers blinded to the outcome of the procedure. There was good agreement between observers in the scoring of each commissure (kappa 0.73 and 0.75 for anterolateral and posteromedial commissures, respectively). Observers agreed on the presence or absence of commissural calcification in all but one commissure (98% concordance, kappa 0.95)

### 8.34 Comparison between TOE and TTE assessment of commissural calcification

In a subset of 33 patients, transthoracic assessment of commissural morphology was compared with TOE findings. Retrospective analysis of video recordings was performed by consensus of two observers. In these elderly patients with degenerative valve disease, optimal visualization of the commissures was not always possible and 6 of the 33 patients (18%) were excluded because of inadequate transthoracic image quality. The majority of these patients had been scanned on earlier ultrasound machines without harmonic imaging capability. The extent of commissural fusion is difficult to quantify reliably by the transthoracic technique and therefore only commissural calcification was evaluated. Using TOE as the 'gold standard', in the remaining 27 patients TTE correctly detected 11 out of 12 calcified commissures (sensitivity of 92%). TTE incorrectly localised leaflet calcification to the commissure in 7 cases (specificity 83%). Interobserver variation for identification of commissural calcification by TTE was 7%.

## 8.4 Results

### 8.41 Outcome from BMV

The mean Wilkins Score was 6.6 (range 3 - 12); 17 patients (24%) had a Wilkins score greater than 8 predicting an unfavourable outcome from BMV. Balloon dilatation of the mitral valve was achieved in all patients and mean MVA assessed by echocardiography increased from 1.1 +/- 0.28 $cm^2$ to 1.8 +/- 0.46 $cm^2$ ($P< 0.01$). Invasive haemodynamic measurements based on the Gorlin formula showed MVA to increase from 0.98 +/- 0.29 $cm^2$ to 1.74 +/- 0.54 $cm^2$

Eight patients (11%) developed severe MR on colour / Doppler echocardiography post-BMV. A good outcome (final MVA >1.5 $cm^2$, >25% increase, no severe MR) was achieved in 40 patients (56%). Patients were divided according to outcome into groups A (good) and B (suboptimal).

### 8.42 Commissure score

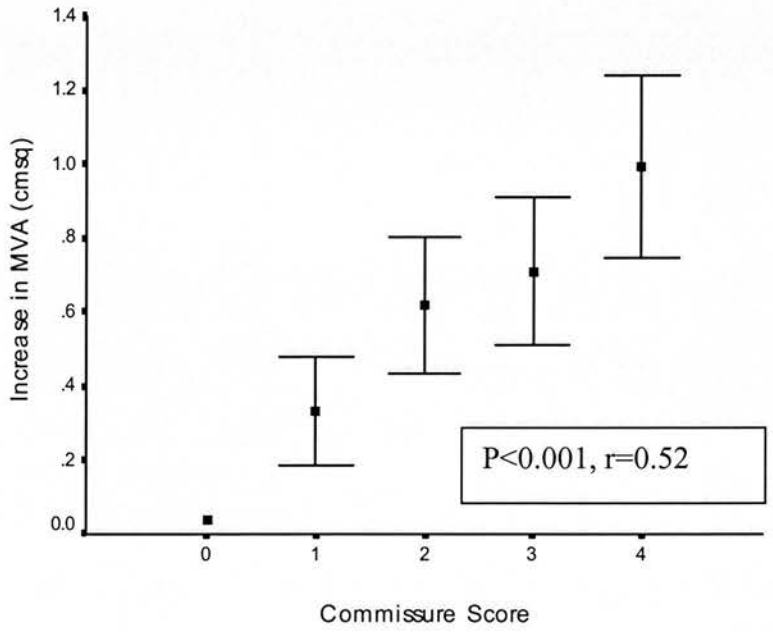
There was a significant correlation between the commissure score and outcome following BMV, higher scores predicting a more favourable result (Table 22, Figure 20). Thirty-seven out of 55 patients with a commissure score of 2 or more obtained a good outcome compared with only 3 patients out of 17 with a commissure score of 0 or 1 (positive and negative predictive accuracy 67% and 82% respectively, $P<0.01$).

**Table 22 Relationship between Commissure Score and outcome.**

| Commissure Score | n | A (Good) n=40 | B (Suboptimal) n=32 | % obtaining good outcome |
|---|---|---|---|---|
| 0 | 1 | 0 | 1 | 0 % |
| 1 | 16 | 3 | 13 | 19 % |
| 2 | 18 | 10 | 8 | 56 % |
| 3 | 20 | 14 | 6 | 70 % |
| 4 | 17 | 13 | 4 | 76 % |

**P<0.01 (chi squared)**

**Figure 20. Correlation between commissure score and the increase in mitral valve area post BMV**



### 8.43 Commissural calcification.

Twenty four patients (33.3%) had calcification localised to either the anterolateral or posteromedial commissure by TOE. No patients had bi-commissural calcification. Commissural calcification predicted a suboptimal result, being present in 18% of group A compared with 53% of group B (P<0.01).

In agreement with results from our transthoracic study of commissural calcification, the incidence of commissural calcium increased significantly with advancing age and also with increasing Wilkins Score (Table 23).

**Table 23: Correlation between baseline variables and commissural calcificatoion**

| | Commissural calcium (n= 24) | No commissural calcium (n=48) | P value |
|---|---|---|---|
| Age (years) | 68 | 58 | 0.001 † |
| Male : Female | 5:19 | 7:41 | 0.5 ✳ |
| Wilkins Score | 7.6 | 6.5 | 0.013 † |
| Commissure Score | 1.4 | 3.1 | <0.001 † |

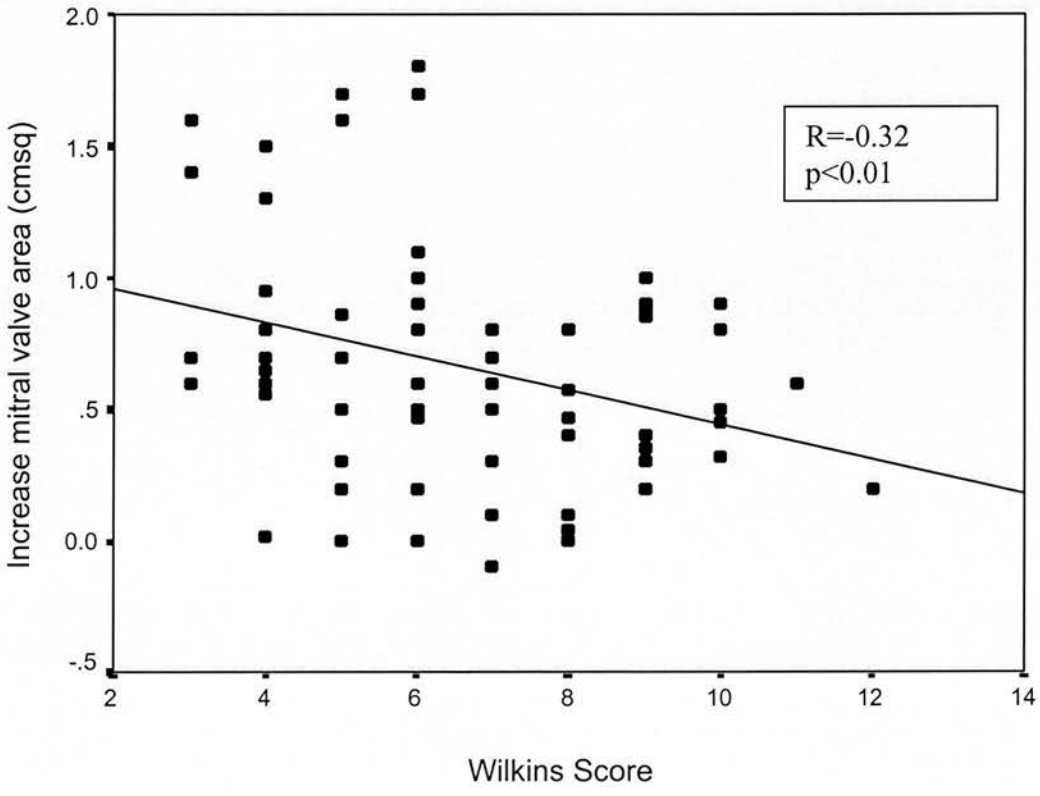
✳ Chi Squared test

† Mann-Whitney Test

### 8.44 Wilkins Score

The Wilkins Score also gave a significant prediction of outcome: mean Wilkins Score 5.9 +/- 2.1 vs 7.4 +/- 2.0 in groups A and B respectively, $p<0.01$. Patients achieving a greater increase in valve area tended to have lower Wilkins Scores, although there was substantial scatter in the data (Figure 21). Using the conventional cut-off of 8, the Wilkins Score was less helpful in predicting good outcome compared with the Commissure Score (positive and negative accuracy of 60% and 59% respectively, p=NS). There was no significant correlation between the Wilkins Score and Commissure Score.

**Figure 21. Correlation between Wilkins Score and increase in valve area**



### 8.45 Multivariate analysis

In a multivariate linear regression model which included age, sex, rhythm, Commissure Score, Commissural calcification and Wilkins Score, Both the Commissure Score ($p=0.0004$) and the Wilkins Score ($p=0.005$) were shown to be independent predictors of outcome from BMV.

### 8.46 Combined assessment of Wilkins criteria and commissural morphology

A combined evaluation of the positive features of valve anatomy (splittable, non-calcified commissural fusion) and negative features (commissural calcification, degenerative change in the leaflets and subvalvar apparatus) helped to further refine the prediction of outcome. In patients with 'good' Wilkins valves (Wilkins Score 8 or less), leaflet and subvalvular change is minimal and severe stenosis is due predominantly to commissural fusion. In such cases the Commissure Score (assessing non-calcified, splittable commissural fusion) was more accurate in predicting outcome. In this group of patients a Commissure Score of 2 or more predicted a good result with positive and negative predictive value of 75% and 80% respectively. In those with 'bad' Wilkins Valves, only 47% of those with a Commissure Score of 2 or more obtained a good result.

### 8.47 Mitral regurgitation

I was unable to demonstrate a significant correlation between Commissure Score and the development of severe echocardiographic MR. The eight patients developing severe MR had a significantly higher Wilkins Score (8.4 +/- 1.9 vs 6.3 +/- 2.1, $p<0.02$). I observed that 4 of the 8 patients who developed severe MR had commissural calcification: in these 4 cases transthoracic echocardiography in the short axis parasternal plane showed the mechanism of mitral regurgitation to be a leaflet tear adjacent to the area of calcification.

## 8.5 Discussion

Commissural calcification was identified in a third of our elderly population and predicted an adverse immediate outcome. Although the Wilkins Score does not specifically assess the commissures, there was a significant correlation between Wilkins Score and commissural calcification. In agreement with the previous transthoracic study, this suggests that degenerative disease of the commissures progresses in parallel with leaflet and subvalvular disease. Heavy generalised leaflet calcification is likely to involve the commissures. For these reasons, the Wilkins Score remains a useful screening tool for patients referred for BMV and in our study was a significant independent predictor of outcome. However, the results of the present study, and those of Fatkin et al, Cannan et al and Sutaria et al, have shown that echo assessment of commissural morphology has important additional predictive value. In our patients, the Commissure Score was a more accurate predictor of outcome than the Wilkins Score.

Two-dimensional TTE remains the most commonly used technique for the assessment of mitral valve morphology and provides a rapid and safe screening tool for the selection of patients for BMV. In the present study, TTE was shown to have a high sensitivity (92%) for detecting commissural calcium. However, in a significant proportion of patients (18%), the commissures could not be adequately visualised. There was a tendency to incorrectly localise leaflet calcium to within the commissure which reduced the specificity (83%). TOE is performed routinely prior to BMV in many centres such as our own. Transoesophageal imaging offers improved resolution and more accurate localisation of calcification than TTE. A semiquantitative assessment of the extent of non-calcified commissural fusion was also made using a previously unreported system. Calcified commissures were shown to be strongly associated with adverse outcome. In cases where one commissure was calcified, absent or minimal fusion of the opposite commissure (commissure score 0 or 1) resulted in a good outcome in only 18%. In the absence of commissural calcium, a low commissure score of 0 or 1 could also arise when mitral stenosis is mild or when stenosis is caused by disease localised to the mitral

leaflets and / or subvalvular apparatus rather than the commissures, a situation not infrequent after a previous surgical valvotomy. In both cases, a satisfactory increase in valve area is unlikely to be achieved by balloon dilatation. Evaluation of commissural fusion as well as calcification should therefore provide a scoring system which more accurately reflects valve splittability. Consistent with this hypothesis, I found a strong correlation between Commissure Score and increase in valve area (Figure 20), $p<0.001$.

Transoesophageal echocardiography is a semi-invasive technique and therefore clear benefits must be demonstrated in order to justify its routine use prior to BMV. A number of studies have compared the relative merits of TTE and TOE in the assessment of patients undergoing BMV. Left atrial thrombus cannot be reliably excluded by TTE due to its inability to fully visualise the left atrial appendage in all patients [Cormier B 1991][Kronzon I 1990][Thomas MR 1992] and TOE is now routinely performed in many centres prior to BMV for this reason. The longitudinal transgastric plane, when available, also allows more detailed visualisation of the chordae and papillary muscles compared with TTE [Rittoo D 1993]. TOE also has a role after BMV since it is more accurate in determining the severity and mechanism of mitral regurgitation and in evaluating the degree of any residual left to right shunting across the interatrial septum [Cormier B 1991].

However, the specific value of TOE in the assessment of commissural morphology has not been demonstrated previously. Other investigators have advocated the use of the transgastric window to obtain an image corresponding to the short axis parasternal view of the valve orifice. However, the mitral valve is conical in shape so the commissures do not lie in a single plane and poor quality images are obtained when there is marked left atrial dilatation. As a consequence, this technique has not been shown to provide adequate visualisation of commissural calcification and fusion [Thomas MR 1992]

In the midoesophageal plane posterior to the left atrium, the mitral valve can scanned at high frequency and is clearly visualised in all patients. We advocate systematic scanning of the anterolateral and posteromedial commissures in the transverse and longitudinal planes, respectively [Rittoo D 1993][Essop M 1991]. A further advantage of TOE over TTE is that acoustic shadowing from leaflet calcification is cast behind the valve into the

left ventricle and is less likely to obscure the orifice, thereby allowing more accurate localisation of mitral calcification. The present study is the first to report the advantages of TOE over conventional TTE for the assessment of commissural calcification and fusion and to demonstrate the value of TOE in predicting procedural outcome following BMV.

It remains that 33% of patients with a high Commissure Score (2 or 3) still failed to achieve a good outcome. This reflects the strict criteria for success used in our study and also suggests that outcome is influenced by multiple aspects of mitral valve morphology. A combined assessment of favourable anatomical features (non-calcified commissural fusion) and unfavourable anatomical features (leaflet and subvalvular change, commissural calcification) is likely to be the best approach for evaluating patients referred for BMV. In accordance, the positive predictive value of the Commissure Score was improved in those patients with 'good' Wilkins valves in whom commissural fusion is the dominant cause of stenosis.

Significant mitral regurgitation is a relatively frequent complication of BMV but one which remains difficult to predict from baseline anatomical and clinical variables [Hernandez R 1992]. A mild increase in MR frequently occurs following BMV at the sites of successful commissural splitting [Fatkin D 1993][Rittoo D 1993][Hernandez R 1992]. In 40 patients studied by Essop et al, the most common cause of severe MR following BMV was shown to be non-commissural tearing of the mitral leaflets. Surgical data from patients undergoing early mitral valve replacement for severe MR following BMV have shown that the mechanism of severe MR usually involves a leaflet tear associated with commissural calcification [Cormier B 1991. Hernandez *et al* noted that as well as commissural calcification, severe subvalvular disease was often found at surgery in patients with severe MR post BMV. This would be reflected in the Wilkins Score which I found to correlate with severe MR. In the present study, commissural morphology was not a significant predictor of severe MR, although half the patients developing MR had commissural calcification.

## 8.6 Conclusions

This is the first study to demonstrate the value of TOE in assessing mitral commissural fusion and calcification in patients undergoing BMV. These factors form the basis of a novel Commissure Score which is reproducible and a useful predictor of immediate outcome after BMV. Application of this scoring system during routine TOE examination prior to BMV could improve patient selection.

Patients with unfavourable commissural morphology (indicated by a Commissure Score of 0 or 1) are less likely to obtain a good result from BMV and mitral valve replacement would need to be considered. Exceptions to this rule might include elderly patients or those with a prohibitively high surgical risk. In such cases, we recommend cautious inflations using smaller size balloons when commissural calcification has been identified, accepting a suboptimal reduction in gradient. Conversely, some elderly patients who were previously regarded as unsuitable for BMV on the basis of their severely degenerative valve disease and high Wilkins Scores, may obtain a good outcome if commissural morphology is favourable.

# CHAPTER NINE

## Three-Dimensional Echocardiography in mitral valve disease

### 9.1 Background

Whilst conventional two-dimensional echocardiography is crucial to our understanding of the complex anatomy and three-dimensional spacial relationships of cardiac structures, it requires the mental integration of a limited number of 2-D imaging planes. This mental 3-D reconstruction is inherently variable according to observer experience and expertise, and can only be described to other clinicians (such as surgeons) rather than displayed reproducibly. The display of cardiac anatomy in three dimensions from any perspective would have clear advantages over conventional two-dimensional imaging and provide an insight into the functional and anatomic properties of cardiac structures. Recent advances in ultrasound and computer technology have been combined such that dynamic three-dimensional echocardiographic imaging is now a practical reality.

Three-dimensional echocardiography (3-DE) has been shown to be more accurate than 2-DE in the quantification of cardiac volumes [Sapin P 1993][Munoz R 2000]. These studies used either manually contoured, static "wire-frame" reconstructions or dynamic "volumetric" automated reconstruction technology that is now commercially available – I have concentrated on the latter methodology in this review. The benefits of 3-DE are particularly well suited to the study of the mitral valve given its complex morphology and the importance of delineating its anatomy precisely in various pathological states. This was demonstrated by Levine [Levine R 1989] who used wire frame reconstruction of the mitral valve to define the 3-D morphology of the mitral annulus and its relationship to mitral leaflet position, thereby clarifying the echocardiographic definition of mitral valve prolapse. The assessment of patients with mitral valve disease is one of the most promising clinical applications of this technology.

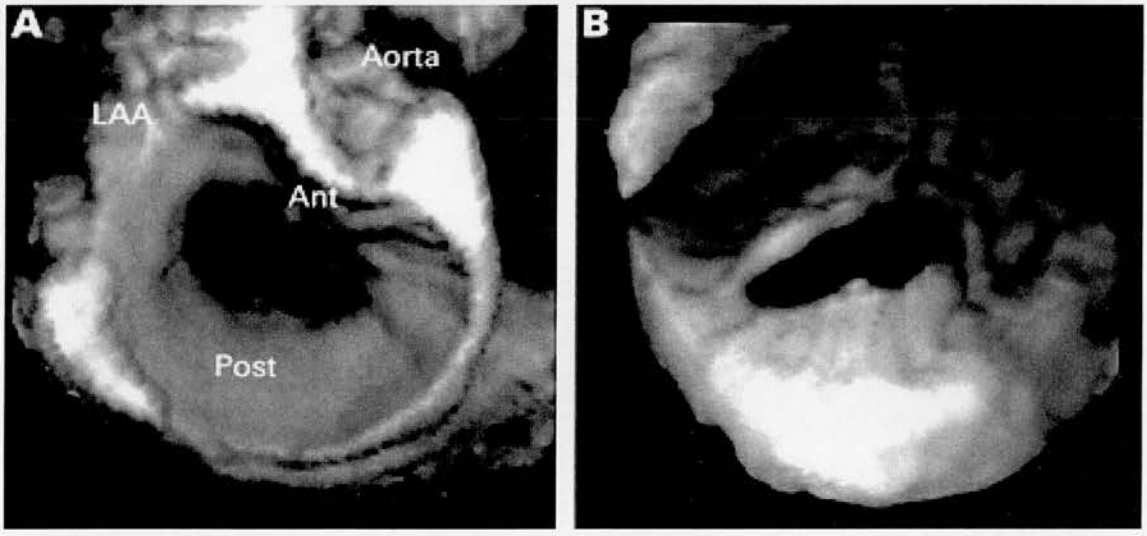
### 9.2 Data set acquisition, processing and reconstruction

A three-dimensional data set is composed of anatomical information from multiple 2-D cross-sectional images. For reconstruction of the mitral valve in adult patients, transoesophageal echocardiography (TOE) is the preferred approach for 2-D image acquisition since it offers a relatively stable site for the imaging probe and superior resolution of the mitral valve apparatus. Images from a commercially available multiplane TOE probe are interfaced with a 3-D computer system which incorporates the steering logic for acquisition of a rotational data set and software for 3-D reconstruction and display. With the mitral leaflets in the transverse mid-oesophageal view, the multiplane TOE probe is usually rotated at 2 or 3 degree increments over 180 degrees to give 90 or 60 sequential 2-D cross sections which are then digitised to form a conical data set [Salustri A,1995]. Optimal temporal and spacial registration is achieved by ECG and respiratory gating. Off-line processing involves the conversion from polar to cubic Cartesian co-ordinates and interpolation of missing information between 2D slices.

From the resultant data set, novel 2-D cut planes in any orientation can be selected (anyplane echo) and multiple parallel cross-sectional 2D slices can be generated in any desired plane (paraplane echo). A volume rendered 3-D image of the mitral valve can be reconstructed from any perspective (Figure 22). Threshold limits are used to separate cardiac structures from blood pool and background. Brightness and shading provide perception of depth. With the added dimension of time I am able to study in detail the motion of the valve during the cardiac cycle.

**Figure 22 3DE of the normal mitral valve.**

3D images reconstructed from the left atrial (A) and left ventricular (B) perspectives, displaying fully the anterior (Ant) and posterior (Post) leaflets and their spacial relation with the aorta and left atrial appendage (LAA).




### 9.3 Three-dimensional echocardiography in mitral stenosis

Three-dimensional echocardiography has a role in both the quantitative and qualitative assessment of mitral stenosis. Paraplane 3-DE allows the 2-D short-axis slice in the optimum plane of the orifice to be selected from the 3-D data set and the smallest complete orifice can be directly measured by planimetry. Anterior leaflet calcification often produces acoustic shadows which obscure the mitral orifice in the 2-D transthoracic short axis plane. Three-dimensional TOE overcomes this problem by visualising the mitral valve from behind such that acoustic shadows are cast into the left ventricle rather than over the leaflet tips. There have been only two small studies, one in abstract form only, investigating the use of 3-DE in measurement of mitral valve area [Chen Q 1997][Kasliwal R 1996]. In the next chapter I report the first in vitro study to validate the accuracy of 3-D TOE for the measurement of mitral valve area.

The shape of the mitral valve leaflets proximal to the orifice has an impact on the flow dynamics across a valve. 3-DE with stereolithographic modelling has been used to demonstrate that flat shaped valves cause a higher pressure gradient for the same anatomic area and flow rate compared with 'funnel' shaped valves [Gilon D 1996]. Thus, 3-DE provides insights into mitral leaflet geometry which could refine our assessment of mitral stenosis.

3-DE also appears to be of value in the assessment of patients undergoing balloon mitral valvotomy, in particular for the evaluation of commissural morphology. Viewed from the left atrium, 3-D reconstruction of mitral stenosis displays the restricted orifice, thickened leaflet margins and prominent left atrial appendage (Figure 23a). In our experience, the volume rendered 3-D display provides improved visualisation of mitral commissural fusion, particularly when the leaflets are viewed from the perspective of looking upwards from the left ventricle (Figure 23b). Following balloon valvotomy, 3-DE also defines clearly the extent and site of commissural splitting which may be symmetrical (Figure 23c) or eccentric (Figure 24). Other investigators have reported improved imaging of the mitral commissures with 3-DE compared with 2-D TOE [Salustri 1996]. Furthermore, 3-DE assessment of commissural splitting following balloon inflation has been shown to relate to increase in mitral valve area.[Applebaum 1998]

**Figure 23 3DE of mitral stenosis.**

3D images reconstructed from the left atrial (A) and left ventricular (B) perspectives. The left ventricular view shows thickened leaflets with a restricted orifice due to symmetrical commissural fusion. (C) shows the same valve after successful balloon mitral valvotomy demonstrating increase in orifice area due to biliateral commissural splitting.

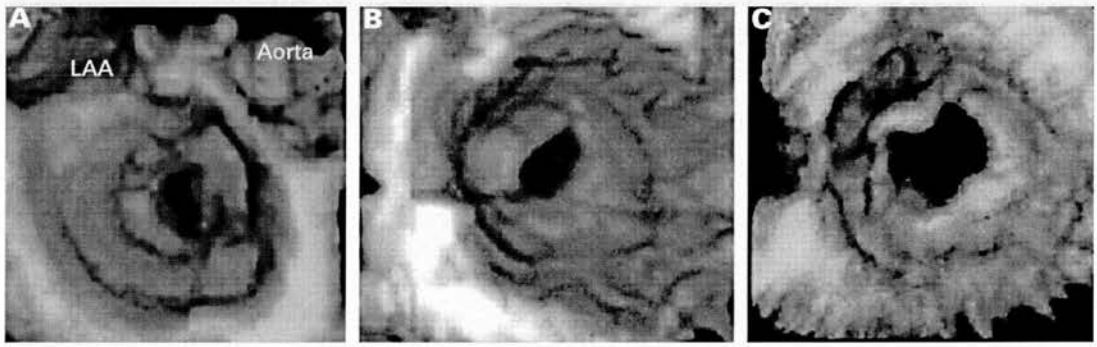
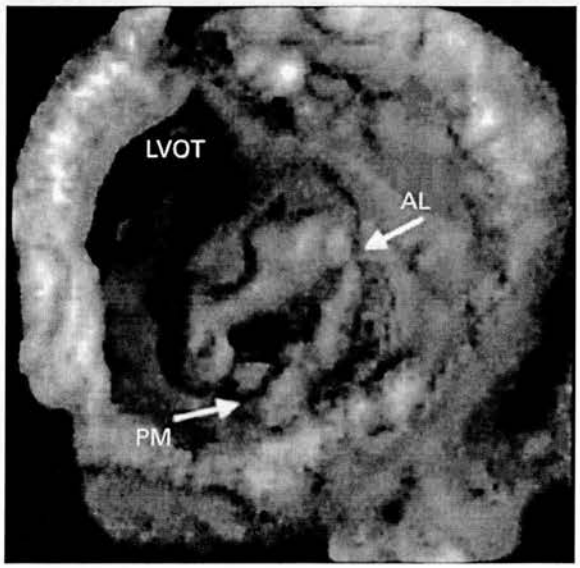



**Figure 24 3DE of mitral stenosis post balloon mitral valvotomy.** 3D image reconstructed from the left ventricular perspective. There has been splitting only of the posteromedial (PM) commissure, the anterolateral commissure (AL) remains fused resulting in an eccentric orifice. LVOT, left ventricular outflow tract.



## 9.4 Limitations of three - dimensional echocardiography

The standard of the 3-D reconstructed display depends critically on the quality of the original 2-D cross-sectional images. Until recently, in adult patients, this necessitated TOE. However, the development of harmonic imaging has made it feasible to reconstruct from a transthoracic rotational data set. Minor movements of either patient or operator will distort the images and result in dropout which may be misinterpreted. Image acquisition is gated to the ECG and respiration: a constant R-R interval and respiratory pattern is ideally required. Variation in R-R interval will lead to a prolonged acquisition time and tachycardia will result in fewer phases per cardiac cycle – both leading to a suboptimal data set. This is often the case in atrial fibrillation, commonly present in patients with mitral stenosis. Patients often have changing respiratory patterns, particularly during intravenous sedation and this also prolongs acquisition time and increases the likelihood of movement artefact.

Operator dependant changes in threshold settings, which define the tissue-blood interface on the 3D rendered display, can affect the apparent mitral orifice. Therefore, measurements on reconstructed images should be made with caution. Spontaneous echo contrast in mitral stenosis hinders reconstruction of the valve from the left atrial perspective, this can be minimised by reducing the probe frequency. Highly mobile structures such as a ball valve thrombus, vegetations and ruptured chords are not well seen. In our opinion, 3-DE has not improved visualisation of the mitral subvalvular apparatus and areas of calcification are not apparent in the volume rendered display. At present this technology provides information which compliments that gained from a comprehensive 2-D and Doppler echocardiographic study.

### 9.5 The future:

In the past, an important limitation of 3-DE has been the prolonged length of time needed for raw data acquisition, data processing and image reconstruction which have made intaoperative studies impractical. However, with improved ultrasound technology and faster digital processing, these problems are being overcome. A rotational 3-D TOE data set can be acquired, processed and displayed within 10 minutes and has been shown to be feasible and useful in the intraoperative setting. 'Real time' 3-D transthoracic probes have been developed and are already commercially available. These factors will enhance the clinical applicability of 3-D echocardiography in the future.

# CHAPTER TEN

# Measurement of mitral valve area using three-dimensional transoesophageal echocardiography: *in vitro* validation (BHF Junior Research FellowshipFS/98072)

## 10.1 Background

Accurate measurement of mitral valve area (MVA) is essential for the management of patients with mitral stenosis. Conventionally, mitral stenosis is quantified by 2D and Doppler echocardiography and also by invasive haemodynamic catheter data. However, as I have discussed previously (section 1.9), all these techniques have important limitations and are imprecise. As yet there is no reliable 'gold standard' for the measurement of mitral valve area.

Three-dimensional echocardiography (3-DE) overcomes the limitations of image plane positioning inherent in 2-DE. By selecting the cut plane in the optimum orientation to the plane of the orifice 3-DE allows more precise planimetry of the limiting mitral valve orifice

There have been only two previous clinical studies, one published only in abstract form, of the application of 3-DE for the measurement of MVA [Chen Q 1997][Kasliwal R 1996] I report the first *in vitro* study to validate the accuracy of 3-D TOE in the measurement of MVA.

## 10.2 Aims:

1.To determine the accuracy and reproducibility of three-dimensional transoesophageal echocardiography (3-D TOE) in the measurement of mitral valve area (MVA) using an *in vitro* model

2. To assess the accuracy of the 3-D reconstruction software in reproducing true valve anatomy

## 10.3 METHODS

### 10.31 Preparation of valves

Forty mitral valves were studied. Thirty five had been isolated from porcine hearts and anterolateral and posteromedial commissures were glued to simulate mitral stenosis. The commissures were glued to varying degrees in order to vary the shape and plane of the orifice and to achieve a gradation of stenosis severity. The latter five valves had been surgically excised from patients with mitral stenosis undergoing valve replacement. All valves were fixed with leaflets in the open (diastolic) position in formalin for 48 hours.

### 10.32 Three-dimensional Echocardiography

**Data set acquisition.**

The prepared valves were mounted on perspex and scanned in a water bath (Figure 25). A 7.5 MHz multiplane transoesophageal echo probe (Acuson TE-V5M) was positioned on the atrial aspect of the valve to obtain a transverse view of the leaflets. Video output from the ultrasound scanner (Acuson 128 XP/10) was interfaced with the 3-D reconstruction system (Tomtec Echoscan, Munich). A rotational 3-D data acquisition was performed as previously described (Section 2.6).

**Analysis of the 3-D data set**

The mitral valve was viewed in the 2-D transverse image plane with clear visualisation of the leaflet tips. A line of intersection was positioned at the tips of both mitral leaflets in the plane of the orifice. This resulted in a short axis image of the valve with optimal orientation to the orifice. Multiple parallel short axis slices at 1 mm intervals incorporating the leaflet tips to the mitral annulus were generated using the paraplane facility. The optimal short axis slice defining the smallest complete orifice was selected for planimetry using Tom Tec software (Figure 26).

**Figure 25 Apparatus for three-dimensional transoesophageal data set acquisition**

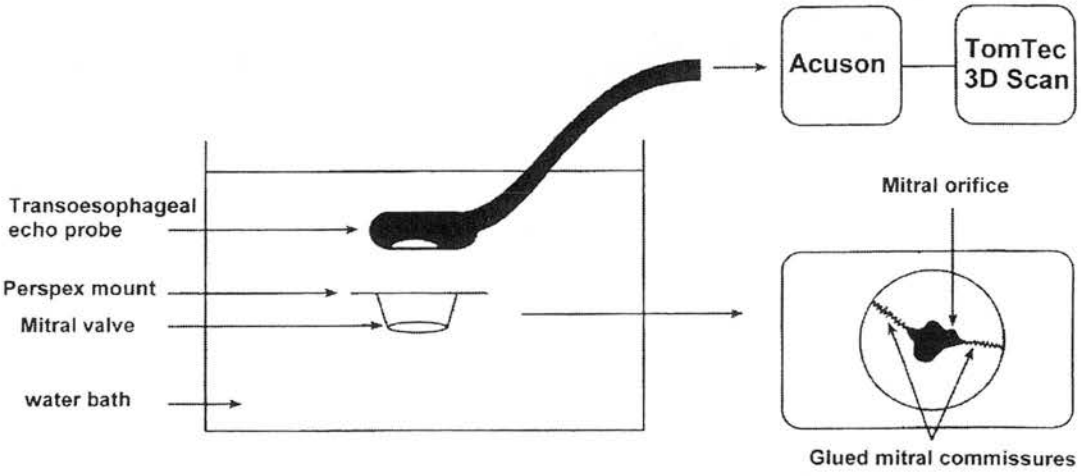
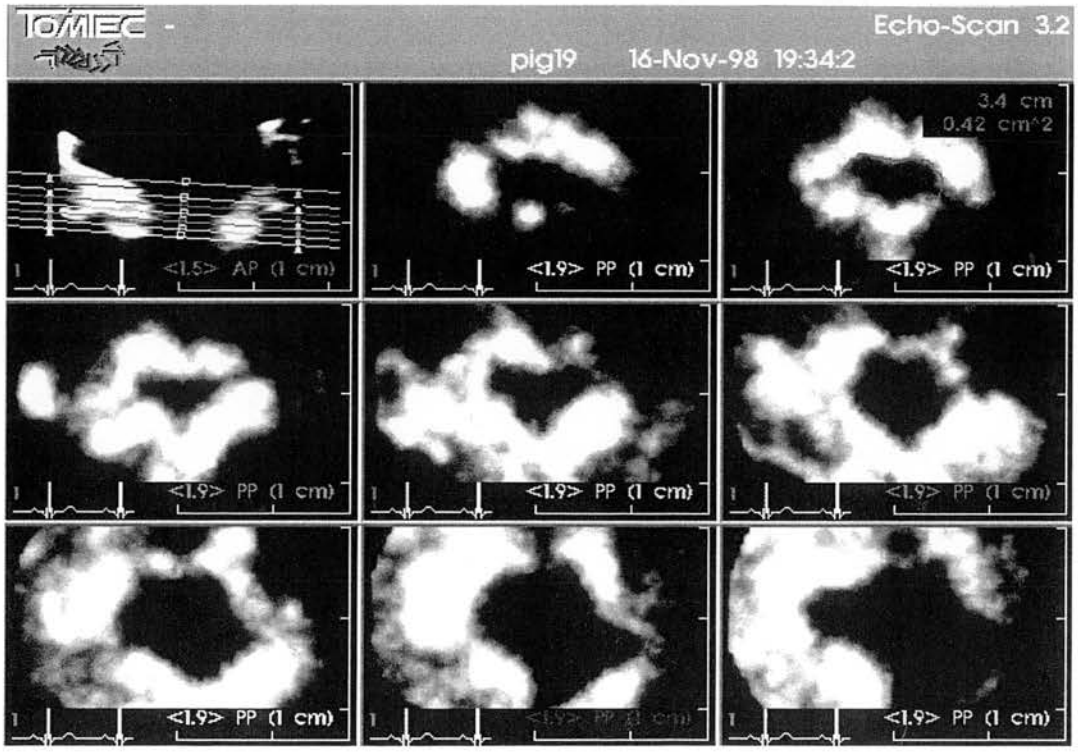



**Figure 26 Planimetry of the optimal 2-D short axis image in the plane of the orifice using paraplane 3-D echo**



Finally, a volume rendered 3-D image of the valve was displayed. This is based on threshold values set by the operator to identify borders of the object of interest and to separate cardiac structures from the blood pool and background. The images were reconstructed in 2 planes (viewed from left atrial and left ventricular perspectives) and compared with the actual anatomy shown by photographic images of the valve.

### 10.33 Determination of reference standard valve area.

The actual or reference standard MVA was determined using a digital photographic technique. The mitral valve was held above a standard flat-bed document scanner (UMAX, Astra 1220P). A parallel light beam from a source 1 metre above was directed through the valve to create a silhouette of the orifice on the surface of the scanner. The valve was angulated in order to project the maximum orifice area. In this position, the valve was scanned at 300 pixels per inch and the orifice area was determined by measurement of pixel intensity in the segmented area of interest using a commercially available computer software package (Paintshop Pro 5, JASC software).

The accuracy of this technique was assessed using 12 cylindrical phantoms of known cross-sectional area ranging from 0.19 to 5.02 $cm^2$. The digital scanner derived areas correlated closely with the actual phantom areas (Mean difference +/- 2SD = -0.004 +/- 0.084 $cm^2$ ) and was deemed to be a reliable reference standard.

Valve areas measured by 3-DE and the reference standard technique were performed by independent operators.

## 10.4 STATISTICS

The correlation between MVA determined by 3-DE and the reference standard technique was studied using the Pearson correlation coefficient and limits of agreement assessed by the method described by Bland and Altman.

## 10.5 RESULTS

### 10.51 Interobserver variability of MVA by 3-DE

Off-line analysis of each 3-DE data set was performed by 2 independent operators with good interobserver agreement: Pearson Correlation Coefficient r = 0.986.

### 10.52 MVA by 3-DE versus reference standard

In 40 mitral valves, MVA determined by paraplane 3-DE ranged from 0.35 - 4.1 $cm^2$ (mean +/- SD: 1.39 +/- 0.80). The reference standard areas ranged from 0.25 - 4.0 $cm^2$ (Mean +/- SD: 1.34+/- 0.79). There was a very good correlation between the areas determined by 3-DE and by the reference standard technique (r = 0.986) with close limits of agreement : Mean difference +/- 2SD (Bland Altman) = -0.05 +/- 0.34 $cm^2$ (Figure 27).

In a heavily calcified human mitral valve, 3-D TOE allowed clear visualisation of the orifice. Despite anterior leaflet calcification, paraplane echo enabled the operator to visualise the optimum 2-D short axis plane of the valve for planimetry without limitation from acoustic shadowing (Figure 28).

### 10.53 Analysis of 3-D volume rendered images

The 3-D reconstructed images were compared with digital photographs of the same valve. The 3-D images displayed accurately the geometry of the mitral valve leaflets and orifice from both atrial and ventricular perspectives (Figure 29).

Figure 27 Bland Altman plot of the difference between MVA determined by 3-DE and reference standard area with mean difference and 95% confidence intervals

**figure 27** Bland Altman Plot of the difference between MVA determined by 3-DE and reference standard area with mean difference and 95% confidence intervals

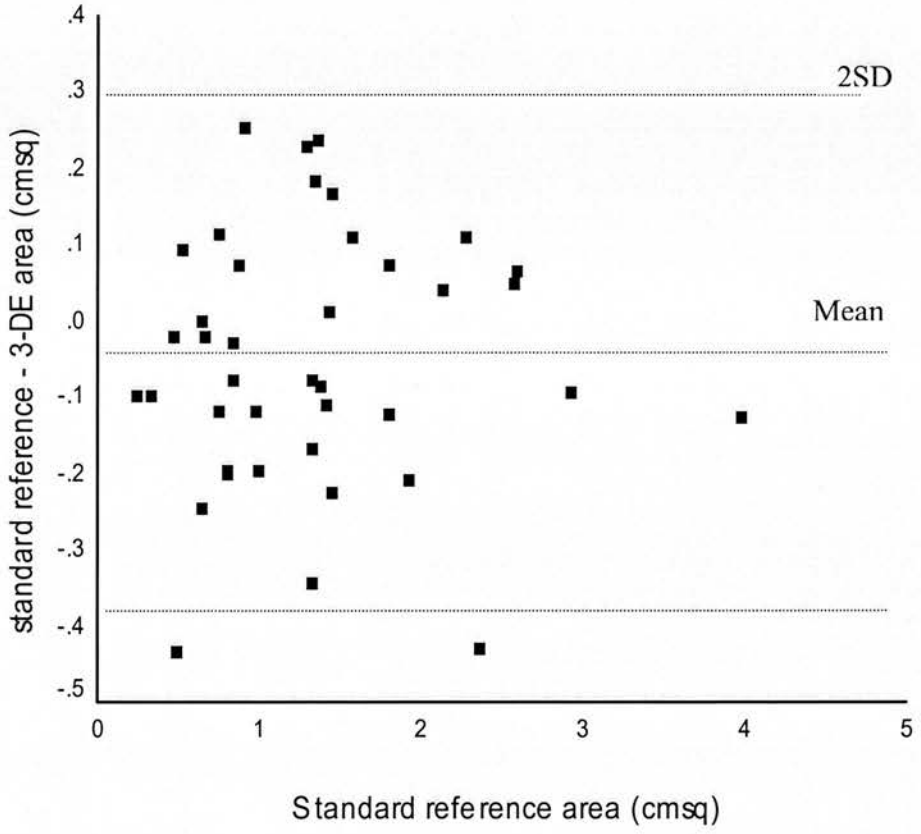



**Figure 28** Calcified excised human mitral valve photographed from the left atrial perspective (A). Anterior leaflet calcification is shown on the 2-D transverse image (B). The 3-D data set allows selection of the optimum 2-D short-axis plane of the orifice for planimetry (C) without limitation from acoustic shadowing.

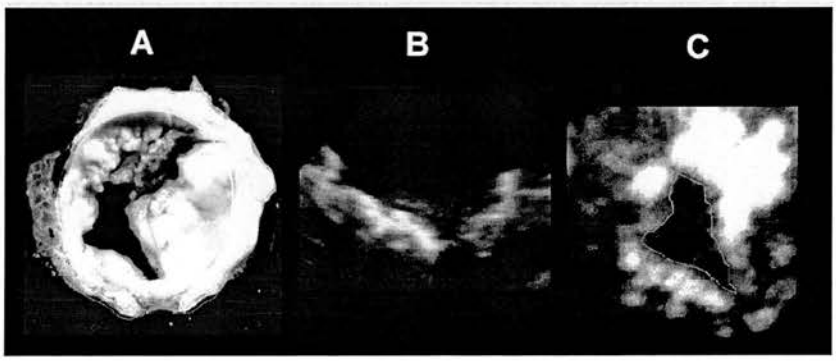
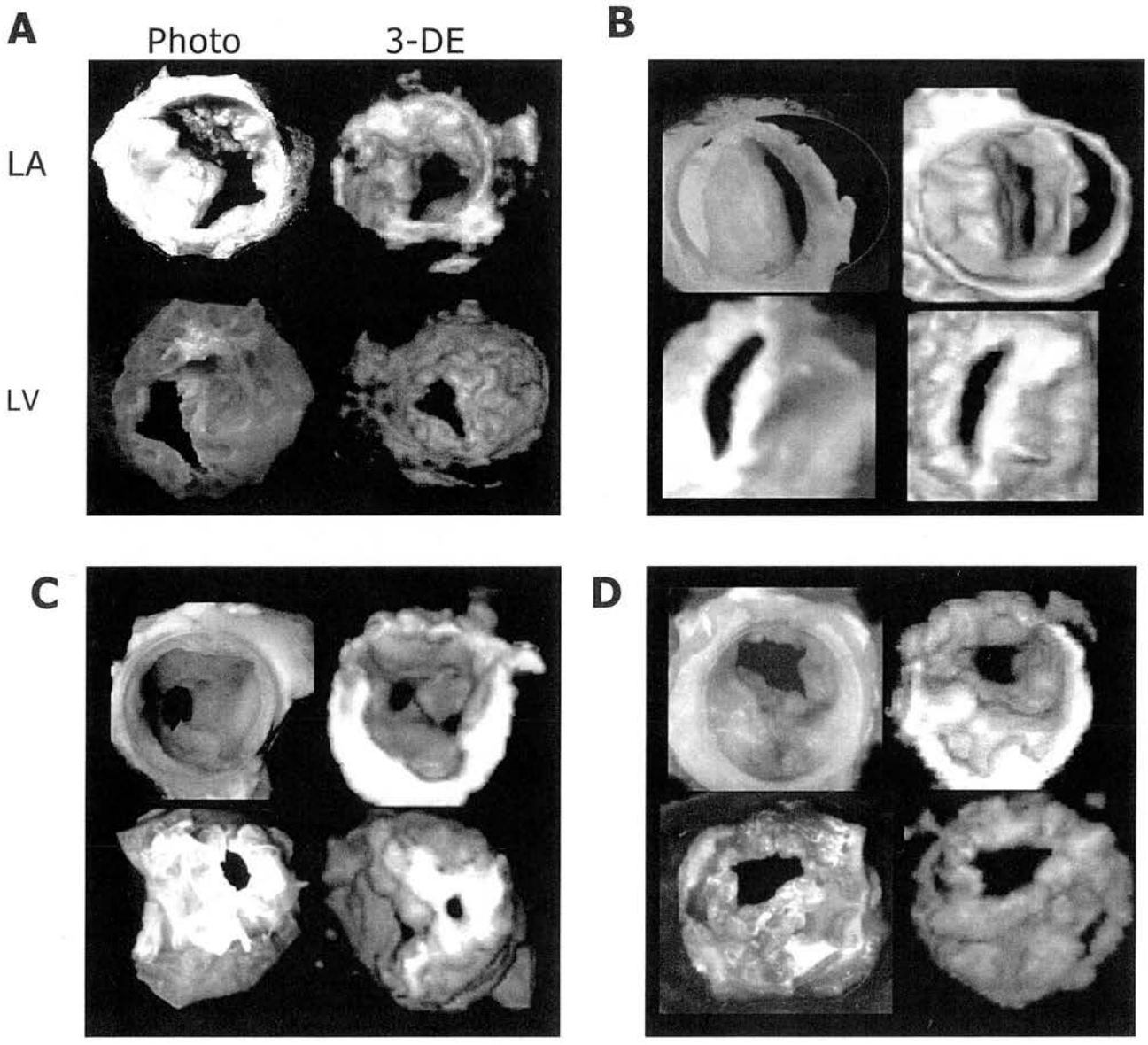


**Figure 29** Comparison between photographic (left) and 3-D reconstructed (right) images of four mitral valves from atrial (top) and ventricular (bottom) perspectives. Figures A and B show excised human valves, C and D show prepared porcine valves.



**Discussion**

There is an increasing demand for more accurate quantitative assessment of heart valve disease. Conventional echocardiography provides excellent qualitative information regarding mitral valve anatomy but lacks accuracy and reproducibility for measurement of mitral valve area. In section 1.7, we have seen how 2-D transthoracic echocardiography is limited by image plane positioning and Doppler pressure half-time becomes unreliable during changes in heart rate and loading conditions. Cardiac catheterisation is still considered the 'gold standard' but is also imprecise and varies with heart rate, rhythm, changes in LV compliance and severity of mitral reflux. Further errors are introduced when the pulmonary artery wedge pressure is used as an indirect measurement of left atrial pressure, or if cardiac output is estimated rather than directly measured.

By eliminating assumptions about image plane positioning and LV geometry which are inherent in conventional 2-D imaging, 3-DE provides a more precise approach to quantitative analysis. Three-dimensional echo allows 2-D cut planes of any orientation to be selected from the original data set (anyplane echo) and can generate multiple parallel 2-D slices in a desired plane (paraplane echo). These facilities could allow precise localisation of the limiting mitral valve orifice and accurate planimetry of mitral valve area. However, there have been only two published studies of the use of 3-DE for measurement of MVA. Chen et al [Chen 1997] assessed 15 patients with mitral stenosis and demonstrated that MVA measured by paraplane 3-DE correlated more closely with the Doppler PHT derived area compared with 2-D planimetry ($r=0.98$ vs $r=0.89$). Acquisition was performed using transoesophageal and transthoracic echo and satisfactory analysis of 3D-E data sets was possible in all patients including those with atrial fibrillation and mild leaflet calcification. However, Doppler PHT is itself an imperfect technique for determining MVA and so this study is limited by its use of Doppler PHT as the gold standard. The second study is published in abstract form only [Kasliwal 1996]. In this report 3-D transoesophageal echo was superior to 2-D transthoracic echo for planimetry of MVA in 54 patients when compared with the valve area measured at surgery with calibrated dilators. This study is limited because surgical

dilators have a circular cross section whereas the mitral orifice is often eccentric in shape. Also measurements of orifice area made at surgery may be quite different to the actual mitral valve area in the physiological setting of a beating heart.

I report the first *in vitro* study to validate the accuracy of 3-D transoesophageal for measurement of mitral valve area using a reliable standard reference for comparison. Our technique for locating the limiting mitral valve orifice is similar to that described in the previous studies. MVA measured by 3-DE was reproducible between operators and correlated very well with the standard reference area with close limits of agreement. Additionally, the volume rendered 3-D image provided accurate qualitative information regarding the valve leaflet and orifice shape.

**Study limitations**

I have assessed the accuracy of 3-D TOE in ideal conditions which allow rapid acquisition of an optimal 3-D data set. Our *in vitro* model avoided the problems of artefact due to patient and probe movement and did not require respiratory or R-R interval gating which prolong the acquisition time in the clinical setting. Severe leaflet thickening and calcification might limit the definition of the orifice margins; this could not be assessed in the porcine valves. Further clinical studies are required to evaluate the general applicability of 3-DE in cardiological practice.

TOE is a semi-invasive procedure which would not be justified for the routine measurement of mitral valve area. Transthoracic 3-DE is a more realistic application of this technique and the recent development of 'real-time' transthoracic 3-DE makes this a very practical proposition. The accuracy of the paraplane echo technique needs to be confirmed using these new transthoracic scanners.

**Conclusions**

3-D TOE is an accurate and reproducible technique for measurement of mitral valve area *in vitro*. This technology is rapidly expanding. 3-D software is being integrated into modern echo machines, faster and more highly automated image processing is becoming available and 'real time' 3-D transthoracic probes are being developed. This will

enhance the clinical applicability of 3-DE which could become the gold standard for measurement of mitral valve area.

# CHAPTER ELEVEN

## Conclusions

Rheumatic mitral stenosis remains the commonest cause of acquired heart disease in children and young adults worldwide. With medical treatment alone, severe mitral stenosis leads to progressive deterioration and death, with only 15% of such patients remaining alive at 5 years. Until the mid 1980s, cardiac surgery was the only option for these patients. In 1984, Inoue introduced balloon mitral valvotomy as a new percutaneous technique which produced equivalent results to surgical commissurotomy without the risks of thoracotomy and general anaesthesia. In contrast to aortic valvuloplasty which is now seldom performed except as a palliative treatment, BMV has been widely used as an alternative to cardiac surgery. The success of BMV in young patients with pliant valves and predominant commissural fusion has been well documented and for such patients this technique has become the treatment of choice.

The disappearance of rheumatic fever in the developed world has dramatically changed the demographics of valvular heart disease. Patients presenting with mitral stenosis to Western centres such as ours are typically elderly. The clinical and anatomical characteristics of this population have been less extensively studied. Furthermore, experience of BMV in this population is limited and there have been no randomised trials of BMV versus surgery in the elderly. Consequently, the role of BMV in older patients remains controversial.

In a centre with the largest experience of BMV in the UK, I report on a series of 405 consecutive patients, mean age 60.7 years, with diverse clinical and anatomical characteristics in whom BMV offered both definitive and palliative treatment options. Symptomatic outcome was recorded in 300 patients over 10 years, representing the largest reported long term study of this age group. Older patients had more severe, symptomatically limiting mitral stenosis but with thickened, calcified valves less suitable for BMV. However, they were also at higher risk from cardiac surgery with

overall 26% being judged as inoperable (59% of those >70). BMV in this population was feasible and safe. The procedure resulted in significant immediate haemodynamic improvement (58% had final MVA>1.5 $cm^2$ without severe MR) and symptomatic gain (81% had improved by at least NYHA class at 3 months). Functional benefit was sustained for a reasonable period of time given the extensive comorbidity (61%, 52%, and 42% remained symptomatically improved without MVR at 1, 3 and 5 years respectively). In the frail elderly, BMV offered short term palliation with a low risk of complications. Even a suboptimal improvement in valve area translated into symptomatic benefit which may be sufficient for many individuals to retain their independence.

Long term symptomatic success from BMV could be predicted from the quality of the initial result (MVA>1.5$cm^2$ without severe MR). This was determined primarily by valve anatomy which can be assessed crudely by grading fluoroscopic calcification and more precisely by echocardiographic scoring of leaflet, subvalvar and most importantly commissural morphology. Careful echocardiographic assessment of mitral stenosis is therefore critical to the selection of patients for BMV. Furthermore, careful evaluation of post-procedural valve area and mitral regurgitation is important to identify those likely to deteriorate rapidly unless MVR is offered.

Evaluation of mitral stenosis was the first clinical application of cardiac ultrasound which remains the most important method for the assessment of patients undergoing BMV. Since commissural splitting is the dominant mechanism underlying BMV, commissural morphology should be an integral part of valve assessment. The Wilkins Echo Score is a useful screening tool used widely to select patients for BMV. However, it does not include commissural assessment. Severe degenerative change in the leaflets and subvalvar apparatus develop in parallel with commissural calcification and patients with very high Wilkins Scores ('bad Wilkins valves') have an adverse outcome. However, one third of patients with a low Wilkins Score ('good Wilkins valve') failed to achieve a satisfactory haemodynamic result and tended to deteriorate rapidly after BMV.

Seventy eight percent of such patients were judged operable and might have been better served by MVR.

Commissural calcification affected nearly one third of patients referred with mitral stenosis, increasing in males, the elderly and those with more severe and symptomatic stenosis. Transthoracic echocardiographic assessment of commissural calcification significantly improved the prediction of immediate outcome in 'good Wilkins valves' and was shown to be the most useful anatomical factor for prediction of long term outcome. Patients with absent or minimal commissural calcification (Commissural calcification Grade <2) and little other degenerative change in the leaflets or subvalvular apparatus (Wilkins Scores <8) were ideally suited to BMV and more likely to enjoy a successful immediate result (68% final MVA >1.5 without MR) and longer term benefit (1,3 and 5 and 7 year survival with improved symptoms and no MVR 84%, 77%, 68% and 60% respectively, median 7.24 years).

Transoesophageal echocardiography is performed routinely prior to BMV primarily to exclude left atrial thrombus. However, using a novel scanning technique I have shown that TOE also offers a more accurate and systematic evaluation of mitral commissural fusion and calcification. The absence of non-calcified (splittable) commissural fusion was very strongly predictive of adverse immediate outcome and superior to the currently accepted Wilkins Score. This role of TOE has not been previously demonstrated and could improve case selection, particularly in those who are poor transthoracic subjects.

Evolving echo technology may help to refine our assessment of mitral stenosis in the future. Three-dimensional echocardiography has provided a new insight into complex cardiac structures such as mitral valve. By overcoming problems of image plane positioning inherent in 2-D echo it provides a highly accurate method for planimetry of mitral valve area in vitro. This application needs to be studied in the clinical setting using real time transthoracic scanners and if problems of speed of acquisition, image quality and motion artefact are overcome, this could become the 'gold standard' for quantification of mitral stenosis. By displaying the valve leaflets in their entirety from any perspective, 3-D echo offers a better display of commissural fusion and splitting which may help to assess the results of BMV. However, commissural calcification is not

identified. Whether 3-D echo adds significantly to the morphological assessment gained by conventional 2-D echocardiography in patients undergoing BMV remains to be seen.

The report of the Royal College of Physicians of London on 'Cardiological Intervention in Elderly Patients'[RCP, 1991] stated that "*The goals of medical intervention are improvement in function and postponement of disability, so extending the period of active independent life*". Percutaneous balloon valvotomy can help to achieve this for many elderly patients. Current methods of echocardiographic assessment are imperfect predictors of outcome in a diverse, elderly population and need refinement. In those patients who are fit for surgery, albeit at enhanced risk, I was able to improve the case selection for BMV by including detailed evaluation of commissural morphology using both transthoracic and transoesophageal echo. Those with a high Wilkins Score or unfavourable commissural morphology are less likely to gain longterm success from BMV and should be offered MVR. In those frail elderly who are unfit for surgery, cautious balloon inflation accepting a suboptimal reduction in gradient may still offer short term palliation of symptoms at low risk and should be attempted if there is any prospect of commissural splitting. Elderly patients with severe mitral stenosis should therefore be referred to a cardiac centre for detailed echocardiographic assessment.

## APPENDIX I

**Wilkins Echo Score, Massachusettes General Hospital**

| *Grade* | *Mobility* | *Subvalvular thickening* | *Leaflet thickening* | *Calcification* |
|---|---|---|---|---|
| **1** | Highly mobile , only leaflet tips restricted | Minimal thickening just below leaflets | Leaflets near normal thickness (4-5 mm) | Single area of echo brightness |
| **2** | Leaflet mid and base move normally | Thickening of chordae extending to one third chordal length | Mid-leaflets normal, considerable thickening of leaflet margins (5-8mm) | Scattered areas of brightness confined to leaflet margins |
| **3** | Valve moves forward in diastole mainly from base | Thickening extends to distal third of chords | Thickening extends through entire leaflet (5-8 mm) | Brightness extends to mid portion of leaflets |
| **4** | No/minimal forward movement of leaflets in diastole | Extensive thickening and shortening of all chordal structures extending to papillary muscles | Considerable thickening of all leaflet tissue (>8-10 mm) | Extensive brightness throughout much of leaflet tissue |

## APPENDIX II

### Publications related to this thesis

1 **N Sutaria**, AT Elder, TRD Shaw. Long term outcome of percutaneous mitral balloon valvotomy in patients aged 70 and over. Heart 2000; 83:433-438

2 **N Sutaria,** D Northridge, TRD Shaw. The significance of commissural calcification on outcome of mitral balloon valvotomy. Heart. 2000 Oct;84(4):398-402.

3 **N Sutaria,** AT Elder, TRD Shaw. Balloon mitral valvotomy for the treatment of mitral stenosis in octogenarians. J Am Geriatr Soc. 2000 Aug;48(8):971-4.

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5 Shaw, T R D, **Sutaria, N**, Prendergast, B. Clinical and haemodynamic profiles of young, middle aged, and elderly patients with mitral stenosis undergoing mitral balloon valvotomy. Heart 2003 89: p. 1430-1436

6 **N Sutaria,** TRD Shaw, DB Northridge. Effect of commissural fusion/calcification on outcome following balloon mitral valvotomy - a transoesophageal study European Heart Journal 1998;19 Supplement (Abst)

7 **N Sutaria,** TRD Shaw, B Prendergast, DB Northridge. Effect of commissural fusion on outcome following balloon mitral valvotomy - a transoesophageal study. Heart Suppl 1 Vol 80. (Abst)

8 **N Sutaria,** TRD Shaw, KAA Fox, P Perry, S Pye, R Barruah, D Northridge. Three dimensional transoesophageal echocardiography for the measurement of mitral valve area: in vitro validation Heart 1999 (81) Supplement P10,31 (Abst)

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