ประสิทธิผลของการขยายลิ้นไมตรัลตีบด้วยการสวนหัวใจผ่านหลอดเลือดดำ:

การศึกษาเปรียบเทียบแบบสุ่มระหว่างบอลลูนชนิดอินุเย

กับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ

นางสมนพร บุณยะรัตเวช สองเมือง

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EFFECTIVENESS OF TRANSVENOUS MITRAL VALVOTOMY:

A RANDOMIZED TRIAL COMPARING INOUE BALLOON

AND METALLIC COMMISSUROTOME

Mrs. Smonporn Boonyaratavej Songmuang

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สมนพร บุณยะรัตเวช สองเมือง : ประสิทธิผลของการขยายลิ้นไมตรัลตีบด้วยการสวนหัวใจผ่านหลอดเลือดดำ: การศึกษาเปรียบเทียบแบบสุ่มระหว่างบอลลูนชนิดอินุเยกับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ. (EFFECTIVENESS OF TRANSVENOUS MITRAL VALVOTOMY: A RANDOMIZED TRIAL COMPARING INOUE BALLOON AND METALLIC COMMISSUROTOME) อ. ที่ปรึกษา : ศาสตราจารย์นายแพทย์กัมมันต์ พันธุมจินดา ; 100 หน้า. ISBN 974-17-1866-7

บทนำ ลิ้นไมตรัลตีบจากไข้รูห์มาติกเป็นโรคที่ยังพบได้บ่อยในประเทศที่กำลังพัฒนารวมทั้งประเทศไทย ทำให้เกิดอาการในผู้ป่วยที่อยู่ในวัยทำงานทำให้เกิดความสูญเสียแรงงาน ปัจจุบันสามารถรักษาโดยการขยายลิ้นไมตรัลโดยใช้บอลลูนชนิดอินุเยเป็นเครื่องมือในการขยาย เนื่องจากบอลลูนอินุเยมีราคาแพง ทำให้ต้องนำไปฆ่าเชื้อและนำกลับมาใช้ซ้ำอีก ต่อมามีผู้ประดิษฐ์อุปกรณ์ขยายลิ้นหัวใจแบบโลหะ โดยสามารถนำไปฆ่าเชื้อและนำกลับมาใช้ซ้ำอีกได้ การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบประสิทธิผลของของการขยายลิ้นไมตรัลตีบด้วยการสวนหัวใจโดยศึกษาเปรียบเทียบระหว่างบอลลูนชนิดอินุเยกับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ

รูปแบบการวิจัย การวิจัยเชิงวิเคราะห์ชนิดมีกลุ่มเปรียบเทียบ โดยจัดแบ่งกลุ่มประชากรแบบสุ่ม โดยผู้ประเมินผลการรักษาไม่ทราบว่าใช้เครื่องมือแบบใด

สถานที่ทำการวิจัย หน่วยโรคหัวใจ โรงพยาบาลจุฬาลงกรณ์

ประชากร ผู้ป่วย 60 รายที่มารับการขยายลิ้นไมตรัลด้วยการสวนหัวใจที่โรงพยาบาลจุฬาลงกรณ์

วิธีการ ผู้ป่วยกลุ่มที่ 1 (30 ราย) ได้รับการขยายลิ้นไมตรัลด้วยการสวนหัวใจผ่านหลอดเลือดดำด้วยบอลลูนชนิดอินุเย กลุ่มที่ 2 (30 ราย) ได้รับการขยายลิ้นไมตรัลด้วยอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ

การประเมินผล ความสำเร็จในการขยายลิ้นไมตรัล โดยกำหนดให้ความสำเร็จในการขยายลิ้นไมตรัลประเมินจากหลังการขยายแล้ว 1. พื้นที่หน้าตัดของลิ้นไมตรัล $\geq$ 1.5 ตร.ซม.(โดยวัดจากการตรวจคลื่นเสียงสะท้อนหัวใจ) และ 2. ลิ้นไมตรัลรั่ว $\leq$ เกรด 2 (โดยใช้การประเมินจากการฉีดสารทึบรังสีตามแบบของเซลเลอร์)

ผลการศึกษา ความสำเร็จในการขยายลิ้นไมตรัลของบอลลูนชนิดอินุเย (37%) กับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ (37%) ไม่มีความแตกต่างกัน (p = 0.5) แต่บอลลูนชนิดอินุเยใช้ได้ไม่เกิน 2 ราย ในขณะที่อุปกรณ์ขยายลิ้นหัวใจแบบโลหะสามารถใช้ได้ไม่ต่ำกว่า 30 ครั้ง

สรุป ประสิทธิผลของบอลลูนชนิดอินุเยกับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะไม่แตกต่างกัน แต่อุปกรณ์ขยายลิ้นหัวใจแบบโลหะสามารถนำกลับมาใช้ได้หลายครั้งเป็นการลดค่าใช้จ่ายในการรักษา

หลักสูตร การพัฒนาสุขภาพ ลายมือชื่อนิสิต .....

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่ออาจารย์ที่ปรึกษา .....

ปีการศึกษา 2545

##4375433930 MAJOR HEALTH DEVELOPMENT
KEYWORD: MITRAL STENOSIS/ INOUE BALLOON/ PERCUTANEOUS VALVOTOMY/ METALLIC/ RANDOMIZED TRIAL

SMONPORN BOONYARATAVEJ SONGMUANG: EFFECTIVENESS OF TRANSVENOUS MITRAL VALVOTOMY: A RANDOMIZED TRIAL COMPARING INOUE BALLOON AND METALLIC COMMISSUROTOME
THESIS ADVISOR: PROFESSOR KAMMANT PHANTHUMCHINDA, M.D. 100 pp. ISBN 974-17-1866-7

Objective: To compare the immediate outcome of percutaneous mitral valvotomy (PMV)using the metallic mitral commissurotome and the Inoue balloon.

Design: Randomized single-blind controlled experimental trial.

Setting: Tertiary care, medical school hospital.

Participants: Sixty adult patients with moderate to severe mitral stenosis who had clinical indications for PMV.

Intervention: The patients were randomized to underwent PMV with either the new metallic device or the Inoue balloon. The echocardiography assessing the mitral valve area and other variables post PMV was performed and collected by a blinded cardiologist one day after the procedure.

Main outcome measures: Success of PMV, define as post-valvotomy mitral valve area (MVA) measured by 2-D echocardiography $\geq$ 1.5 cm^2 and mitral regurgitation (MR) severity Sellers' grade < 2.

Results: The success rate was not different between the metallic commissurotome and the Inoue balloon (37% vs. 37%, p 0.5). The post-PMV MVA in the Inoue group was 1.38 $\pm$ 0.28 cm^2 vs. 1.47 $\pm$ 0.33 cm^2 in the metallic commissurotome (p 0.26). Procedural failure in the Inoue group was mainly (18 patients) from post-PMV MVA < 1.5 cm^2 and 1 patient developed severe mitral regurgitation. Whereas causes of failure in the metallic commissurotome were crossover in 4 patients, 12 post-PMV MVA < 1.5 cm^2,1 had severe mitral regurgitation and 2 had cardiac tamponade. The same metallic commissurotome could be used in all 30 patients. On the other hand, 23 Inoue balloon were used in the 30 patients.

Conclusion: The success rate of PMV is not different between metallic commissurotome and Inoue balloon. Complications with metallic commissurtome tend to be more serious. However, the cost effectiveness is better with the metallic commissurotome.

Department Health Development Student's signature ……..……..……

Field of study Health Development Advisor's signature……..……..……..

Academic year 2002

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CHAPTER 1

INTRODUCTION

Background and Rationale

In developing countries, rheumatic fever is one of the important health problems, which may result in rheumatic heart disease in the long term. The disease usually causes symptoms and disabilities including rheumatic mitral stenosis in young adults. In the past, rheumatic mitral stenosis patients have to undergo surgical commissurotomy to relieve the valvular obstruction, or have the valves replaced. However, the treatment of choice for symptomatic rheumatic mitral stenosis patients with suitable valvular morphology is percutaneous mitral valvotomy . The technique has the advantage over surgery because it is less invasive and the patients can be discharged one day after the procedure.

The first report of percutaneous balloon mitral valvuloplasty by Inoue et al[1] came in 1984. Since then, the technique has become an accepted alternative to surgical commissurotomy, leading to comparable immediate and long-term results.[2, 3]

However, the cost of the procedure, which results principally from the cost of the balloon catheter used, still remains a limitation to its application in developing countries with limited financial resources. These countries have the highest incidence of mitral stenosis. Consequently, most centers in developing countries reuse these balloon catheters several times, although they are provided as disposable catheters; this introduces potential hazards because of imperfect sterilization and decreasing performance caused by the alteration of the balloon's mechanical properties.

Results Of Percutaneous Mitral Valvotomy With The Inoue Balloon In King Chulalongkorn Memorial Hospital

From January 1993 through December 1997, 145 patients underwent percutaneous mitral balloon valvotomy with the Inoue balloon. The mean age was 36 $\pm$ 11 years and 81% of the patients were female. The mean echocardiographic score was 7.4 ± 1.6 (range 4 to 12). The procedure could be completed in 142 of the 145 patients (98%) and failed in 3. In all 3 patients, it was not possible to puncture the interatrial septum. The mitral valve area increased from 0.79 ± 0.18 to 1.38 ± 0.28 cm^2 ($p < 0.001$, 95% CI 0.53 – 0.63 cm^2). However, the post-valvotomy mitral valve area was less than previously reported in the literature (usually in the range of 1.7 to 2.0 cm^2).[2, 4, 5] Moreover, the success rate, defined as valve area $\geq$ 1.5 cm^2 with mitral regurgitation $\leq$ grade 2, could be achieved in only 35% of our patients (compare to about 80 to 95% from the literature).[6-8] Most of the patients had symptomatic improvement but long-term outcomes of these patients have not been investigated.

One possible explanation for the low success rate was the reuse of the Inoue balloon. The manufacturer recommended disposing the balloon after single use. We had to reuse the balloon otherwise the procedural cost would be very high (Inoue balloon price was 96,000 baht per balloon and can be reused for very limited times). Since the balloon was made from meshed polymer and latex, the material had the potential to lose its strength and integrity with the repeated re-sterilization.

Recently, Cribier et al [9] developed a percutaneous valvotomy device featuring a metallic valvotome (Overture™, THB 250,000), the principle of which is similar to the metallic device (Tubbs dilator) used by surgeons for closed chest mitral commissurotomy. This device acts mainly by

stretching and subsequent separation of the commissures. Once the device is opened across the mitral valve, the catheter shaft rotates by itself in such a way that the bars are directed to the commissures. That property is proposed to improved efficacy. Another main advantage of this device is that it can be reused several times without any loss of performance after proper resterilization, and thus it decreases the procedural cost.

The main objective of this study is to systematically compare the effectiveness between transvenous mitral valvotomy using the conventional Inoue balloon and transvenous mitral valvotomy with the new device, metallic commissurotome. The secondary objective is to compare the reusability of the devices and cost.

CHAPTER 2

REVIEW OF RELATED LITERATURES

Definition of Mitral Stenosis

Mitral stenosis is defined as obstruction of left ventricular inflow at the level of mitral valve. It is a result of a structural abnormality of the mitral valve apparatus, preventing proper opening during diastolic filling of the left ventricle.

Etiology

The predominant cause of mitral stenosis presenting in adulthood is a progressive reaction to injury from prior rheumatic fever of streptococcal infection. Isolated mitral stenosis occurs in 25% to 40% of all patients with rheumatic heart disease, and a history of streptococcal infection can be elicited in more than 60% of patients with mitral stenosis.[10, 11]

Congenital malformation of the mitral valve occurs rarely and is observed mainly in infants and children. Other rare causes of valvular mitral stenosis include systemic carcinoid, systemic lupus erythematosus, rheumatoid arthritis, the mucopolysaccharidosis, methysergide, amyloid deposit and fenfluramine/phentermine therapy. Cor triatriatum and atrial myxoma also cause obstruction to inflow and can simulate mitral stenosis. Another etiology of mitral stenosis observed with increasing frequency in degenerative calcific disease in the elderly. The calcification generally involves the annulus and the aortic root and extends into the valve leaflets. However, the free margins are spared and the resulting mitral stenosis is usually mild.

Pathology

In patients with mitral stenosis caused by rheumatic fever, characteristic findings include leaflet thickening and calcification, commissural fusion, chordal fusion, or a combination of these processes.[12] These changes result in a distorted mitral apparatus and decreased size of the mitral valve orifice shape like a “fish mouth” or buttonhole. Commissural fusion is responsible for narrowing the principal orifice and interchordal fusion for obliterating the secondary orifice.[13]

Pathophysiology

The normal mitral valve opens to an area of 4 to 6 cm^2. Narrowing of the valve area by the rheumatic process to < 2.0 to 2.5 cm^2 must occur before any symptoms develop.[14] Narrowing of the mitral valve orifice results in obstruction to the left ventricle inflow and blood flow has to be actively propelled from the left atrium across the narrowed orifice to the left ventricle in order to maintain an appropriate cardiac output. This results in a diastolic transmitral gradient, which is the hallmark of mitral stenosis.[15] As a consequence, there is an elevation of left atrial pressure that may in turn be transmitted to the pulmonary venous circulation and give rise to pulmonary congestion. The left atrial mean pressure can reach 25 mmHg when the orifice of the mitral valve is reduced to approximately 1.0 cm^2. Another major circulatory change is reduction of blood flow across the stenotic mitral valve; i.e. reduction of the cardiac output. The normal resting cardiac output of 3.0 litres/min/m^2 usually falls to about 2.5 litres/min/m^2 when the valve size is 1.0 cm^2.[16]

Pulmonary hypertension frequently complicates mitral stenosis. The pathophysiology of elevated pulmonary artery pressure is complex.[17] This may result from a "passive" hypertension caused by elevated left atrial pressure. Also pulmonary vascular changes may occur from vasoconstriction mediated by neurohumoral factors, such as endothelin [18], or from true anatomic remodeling, that is, medial hypertrophy and intimal thickening. [19] The increased pulmonary arteriolar resistance may actually be an adaptive mechanism to protect the lungs from severe pulmonary congestion.[20] With increasing hypertension, an increase in right ventricular end-diastolic volume and pressure, as well as secondary tricuspid regurgitation, may develop, which may results in right-sided heart failure and systemic venous congestion.

Severity

The severity of mitral stenosis on the basis of valve area has been graded mild, moderate and severe (Table 2.1).

Table 2.1 Grading of mitral stenosis severity based on the mitral valve area and mitral valve gradient

	Area	Pressure Gradient
Mild	> 1.5 cm^2	< 5 mmHg
Moderate	> 1 and < 1.5 cm^2	5 – 10 mmHg
Severe	<1 cm^2	> 10 mmHg

A mitral valve area >1.5 cm^2 is usually not associated with symptoms at rest.[21] The first symptoms in patients with mitral stenosis are usually precipitated by factors that either increase flow rate or cardiac output or decrease the diastolic filling period and therefore markedly raise left atrial

pressure. These include the following: (1) exercise, (2) emotional stress; (3) infection; (4) pregnancy, or (5) atrial fibrillation with rapid ventricular response.[21] As the orifice size decreases, the left atrial pressure will rise with concomitant progression in symptoms.

Natural History

Mitral stenosis is often a continuously progressive, lifelong disease. It is a disease of plateaus initially manifesting with only the signs of mitral stenosis followed years later with the onset of symptoms, then atrial fibrillation and finally disabling symptoms (Figure 2.1).[10, 22] From studies in the pre-surgical era, it is clear that there was a long latent asymptomatic period of 10 to 30 years

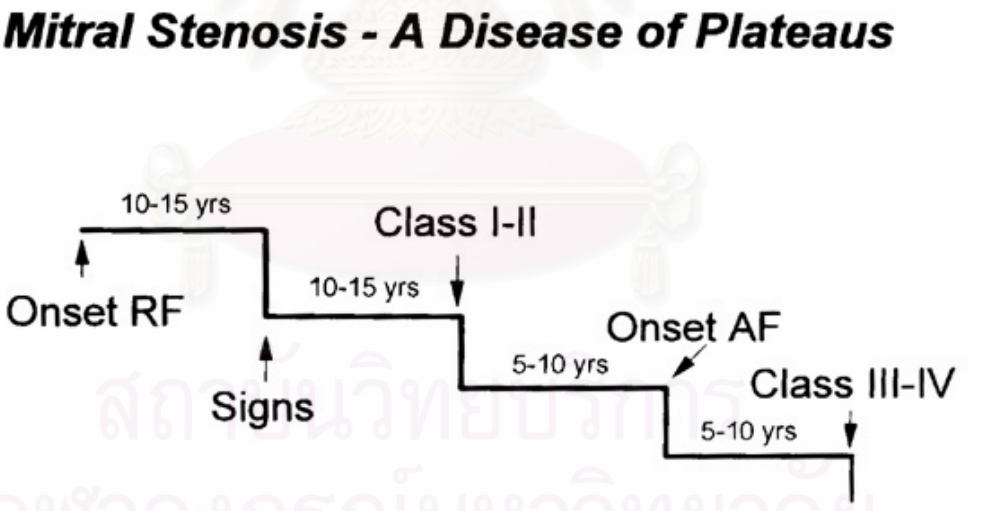


Figure 2.1 Schematic diagram illustrates that mitral stenosis is "a disease of plateaus." There is a long asymptomatic period of 10 to 30 years after the initial attach of rheumatic fever until the development of class I to II symptoms. In North America the latent period may be even longer. Once symptoms develop there is a plateau of 5 to 10 years before the onset of atial fibrillation or until symptoms become disabling. With the development of class III to IV symptoms, the prognosis if grim, with a 15% 10-year survival rate.

after the initial attack of rheumatic fever until the development of symptoms. The overall 10-year survival rate of untreated patients with mitral stenosis is 50% to 60%. If no or minimal symptoms exist, this 10-year survival rate is as high as 80%. Sixty percent of these patients will have no progression of symptoms. However, once symptoms develop there is a plateau of 5 to 20 years before these become disabling. With the cardiac rhythm change from to atrial fibrillation the overall prognosis is less good (25% 10-year survival rate) than patients who continue to be in normal sinus rhythm (46% 10 year survival rate).[23] The risk of arterial embolization is also significantly increased in patients with atrial fibrillation.[24]

Clinical Manifestations

History

Many patients with mitral stenosis will be symptom free. The chief complaint of patients with symptoms of mitral stenosis is dyspnea. They may have paroxysmal nocturnal dyspnea, orthopnea or even pulmonary edema. This may be precipitated by any conditions that increase blood flow across the stenotic valve or that reduces diastolic filling time as mentioned above. Fatigue is a common symptom from low cardiac output or inability to augment cardiac output with exertion.

Atrial arrhythmias can develop in 30% to 40% of otherwise asymptomatic patients. Atrial fibrillation tends to be provoked by age and distention of the left atrium which alter the electrophysiologic properties of the left atrium.

Occasionally patients may have episodes of hemoptysis and usually associated with end-stage severe mitral stenosis and is rarely seen today.[10] Chest pain occurs in about 15% of the

patients and may be difficult to differentiate from angina pectoris.[10] It is believed to result from right ventricular hypertrophy and rarely from concomitant coronary atherosclerosis.

The initial presentation may be a complication of mitral stenosis. Such complications include thromboembolism, infective endocarditis, or even compressive symptoms of dysphagia or hoarseness form an enlarged left atrium.[10]

Physical Examination

The classic findings on examination of a patient with mitral stenosis are the opening snap and diastolic rumbling murmur.[10] The presence of a loud S1 and a crisp opening snap indicate that the mitral leaflets are pliable.

Investigations

Electrocardiogram (ECG)

The ECG is a relatively insensitive technique for the detection of mild stenosis, but in patients with hemodynamically significant obstruction characteristic features are P mitral (defined as a widened P wave of > 0.12 seconds with normal or only slightly increased voltage, usually notched , bifid or flat-topped) is a sign of long-standing mitral valve disease and is typically present in all, cases of stenosis severe enough to warrant valvotomy. Right ventricular enlargement is closely related to pulmonary vascular resistance and suggests that the stenosis warrants intervention .

Chest Roentgenogram

The classic x-ray appearance of mitral stenosis reveals left atrial enlargement, pulmonary artery enlargement, and varying degrees of pulmonary congestion.[10] Interstitial edema, an

indication of severe obstruction, may manifest as Kerley B lines and in found in 30% of patients with resting left atrial pressure <20 mmHg and in more than 70% of patients with a pressure > 20 mmHg.[25] Other features include Kerley A lines, hemosiderosis and mitral valve calcification.

Two-dimensional and Doppler Echocardiography

Two-dimensional and Doppler echocardiography is now the diagnostic modality of choice for evaluation of patients with mitral stenosis. Two-dimensional echocardiography can visualize mitral valve structure and motion and thus establish the diagnosis, provide an estimate of severity of stenosis and determine suitability for valvotomy procedure.[26-28] In addition, Doppler echocardiography provides measurement of valve gradient and valve area.[29] Additional information such as chamber size and function, the presence and severity of other valvular lesions and pulmonary pressure can also be obtained noninvasively. Finally, changes in hemodynamics with interventions such as exercise or dobutamine infusion can be measured.[30, 31]

Measurement of Mitral Valve Area

There are many ways to measure the mitral valve area (Table 2.2). In the early era, the mitral valve area usually is measured from the mitral valve specimens, either from autopsy or during surgery. This method has limitations because of the invasive nature and cannot be applied in everyday practice. However, the valve area by pathology or during surgery served as a gold standard against the subsequent measurement by cardiac catheterization and echocardiography.

Table 2.2 Methods for Measurement of Mitral Valve Area

1.	Measurement from pathologic specimen (valve excised from autopsy or surgery)
2.	Measurement during surgery
3.	Measurement from cardiac catheterization
4.	Measurement by echocardiography
	4.1. Two-dimensional echocardiography (planimetry method)
	4.2. Doppler echocardiography
	4.2.1. Pressure-half time
	4.2.2. Proximal isovelocity area (PISA)
	4.2.3. Continuity equation

Measurement of Mitral Valve Area by Cardiac Catheterization

Cardiac catheterization was considered to he the standard for assessing mitral valve hemodynamics in the past. However, the two-dimensional and Doppler echocardiography has now taken over the role of diagnosis and hemodynamic assessment in patients with mitral stenosis. The catheterization laboratory is now used primarily for treatment of patients with mitral stenosis (i.e., percutaneous mitral balloon valvotomy). Invasive hemodynamics are reserved for the rare patient in whom further information is required after a comprehensive two-dimensional and Doppler assessment.

The hallmark of the severity of mitral stenosis is the transmitral gradient. Accurate measurement of the transmitral gradient requires simultaneous left atrial and left ventricular

pressures. Direct measurement of left atrial pressure is usually performed through a transseptal puncture, which requires experience and expertise to avoid the potential complications of aortic puncture, tamponade, and heart block. The development of the pulmonary artery wedge pressure has now provided an indirect method for measuring left atrial pressure from a right-sided heart catheterization and is now used by most laboratories when mitral valve hemodynamics are obtained.[32] However, there are many potential errors, which may occur when using pulmonary artery wedge pressure.

The standard accepted approach to obtain a proper pulmonary artery wedge pressure is to use a large-bore end hole catheter. The end hole is firmly "wedged" into a distal pulmonary artery, and a saturation of >95% is required to confirm a proper wedge position. Most laboratories today use a balloon-tipped catheter with thermodilution cardiac output capabilities for right-sided heart measurements. Although this provides more convenience in terms of catheter manipulation and simultaneous cardiac output measurements, this catheter has a small internal lumen that may not provide reliable pulmonary artery wedge pressure, especially when saturation confirmation is not performed. A dampened pulmonary artery pressure waveform may simulate a true pulmonary artery wedge pressure, causing a significant overestimation of the transmitral gradient.[32]

Even with properly performed and confirmed pulmonary artery wedge pressure, a 40% to 70% overestimation of transmitral gradient may occur. This is usually due in part to a delay in the transmission of pressure. However, even when there is a correction for the time delay, a pulmonary artery wedge pressure can overestimate the transmitral gradient by up to 50% because of a slowed rate of fall of the "Y" descent after the onset of mitral valve opening. A Doppler-derived transmitral gradient is a reproducible and reliable measurement that is more accurate than the gradient

obtained by catheterization with a pulmonary artery wedge pressure and left ventricular pressure.[32] Therefore catheterization should not be relied on strictly for measurement of the transmitral gradient in patients with mitral stenosis because this can be accurately obtained noninvasively. Another measurement frequently obtained at cardiac catheterization is a calculated mitral valve area The mitral valve area is calculated from the original Gorlin equation [14] with modification by Cohen et al. [33]

$$\mathbf{MVA} = \frac{\mathbf{CO}}{\mathbf{HRxDFTx}\,37.9\mathbf{x}\sqrt{\Delta\mathbf{P}}}$$

This derived valve area has multiple limitations (Table 2.3). The constant incorporates an empiric coefficient of discharge, which may not hold up under varying hemodynamic conditions or differing orifice slopes. A quadratic relationship may not exist between pressure and flow, as is assumed in the Gorlin equation, particularly in the low-flow states. Cardiac output measurements may be inaccurate, particularly when the commonly used thermodilution method is used in the presence of atrial fibrillation or concomitant tricuspid regurgitation. As noted above, there may be significant errors in measurement of the mean transmitral gradient if pulmonary artery wedge pressure is used. The hydraulic equation is inaccurate at low or high heart rates. Concomitant mitral regurgitation will cause an overestimation of the severity of stenosis from a calculated valve area.

For all these reasons, a catheterization-derived valve area should not be relied on as a single measurement of the severity of mitral stenosis.

Measurement of Mitral Valve Area by Two-dimensional Echocardiography

The diagnosis of mitral stenosis can be reliably made from two-dimensional echocardiography that demonstrated restricted opening of the mitral valve leaflets with diastolic doming of the anterior leaflet and immobility of the posterior leaflet. The anterior leaflet will classically have a “hockey-stick” deformity in diastole when visualized from the parasternal long-axis view. A fish-mouth” appearance of the opening of the mitral valve leaflets is seen on the parasternal short axis view.

The severity of mitral stenosis may be determined from two-dimensional echocardiography by direct measurement of a valve area. The office of the mitral valve can be visualized on the parasternal short-axis view. Most of the current two-dimensional echocardiographic equipment will allow for the image to be frozen in early diastole at the time of maximum mitral valve opening. This is performed from capturing a cardiac cycle in a cine loop format. The area can be measured with planimetry by use of on-line with internal software directly on the echocardiographic machine (Figure 2.2).

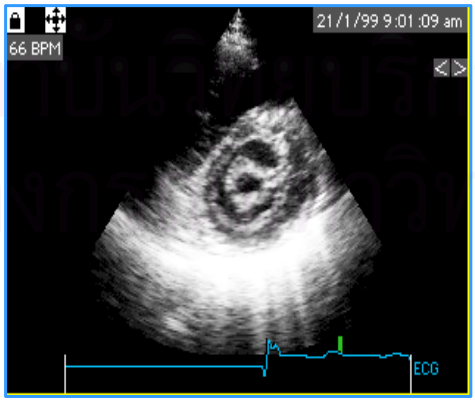


Figure 2.2 Two-dimensional echocardiography demonstrated the short axis at the mitral valve level. Mitral valve area can be obtained by planimetry of the orifice area.

Image resolution is critical for two-dimensional echocardiographic determination of mitral valve area, and this measurement should not be performed if there is a suboptimal parasternal window. Changes in gain may cause discrepancies in the measured mitral valve.[28] In the presence of calcification of the mitral valve leaflets, acoustic shadowing may prevent accurate determination of area. Because the mitral valve leaflets will dome in diastole, overestimation of mitral valve area may occur if the plane of the short axis is not at the exact tip of the mitral valve leaflets but located more superiorly at the level of the body of the leaflets. Thus the mitral valve area can be prone to error and should only be reported by laboratories with experience and expertise in this measurement.

Measurement of Mitral Valve Area by Doppler Echocardiography

The transmitral gradient is measured from continuous-wave Doppler interrogation of the diastolic flow across the mitral valve. By applying the modified Bernoulli equation (pressure gradient = 4 x velocity^2): an instantaneous gradient between left atrium and left ventricle is determined. Software calculation packages on current echocardiographic machines now allow calculation of the mean gradient.

The jet of mitral stenosis is almost always central and directed toward the left ventricular apex (Figure 2.3). Therefore the pitfall of determining accurate pressure gradients seen with other valvular lesions can be avoided. In other valvular lesion, the underestimation of gradient can result from a large angle of incidence between the Doppler beam and stenotic jet.

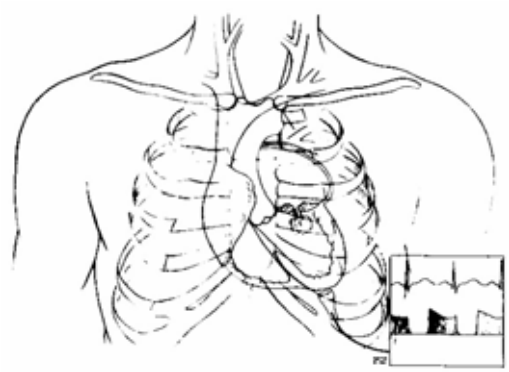


Figure 2.3 Diagram demonstrates continuous wave Doppler determination of transmitral flow velocity.

The most common method of determining mitral valve area by Doppler echocardiography is the diastolic half-time method. The half-time is a measurement of rate of pressure drop between the left atrium and left ventricle that was originally applied to catheterization pressure measurements. It was observed that as the severity of mitral stenosis increased, there was a proportional slower rate of pressure decline between left atrium and left ventricle. The half-time was defined as the time it took for the peak initial pressure gradient to drop by 50%. A half-time longer than 300 msec was considered to indicate severe mitral stenosis at catheterization. The diastolic half-time was found to he independent of the preceding cycle length and useful in patients with in irregular rhythms such as at atrial fibrillation. It was also independent of coexistent mitral regurgitation. The half-time method was shown to be more accurate than the Gorlin formula at cardiac catheterization in patients with concomitant severe pulmonary hypertension. This increased accuracy of the half-time method in patients with severe pulmonary hypertension was probably related to the inaccuracies of the pulmonary artery wedge pressure in these patients.

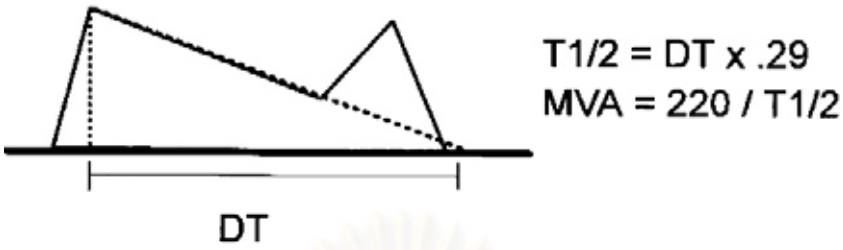


Figure 2.4 Diagram demonstrates the pressure-half time measurement of the signal obtained by continuous-wave Doppler

A measurement of diastolic half-time can he measured from the transmitral flow velocity curve obtained from Doppler echocardiography by use of the "deceleration time" (Figure 2.4). The "deceleration time" is measured by extrapolating the deceleration of flow to the baseline and measuring the time from peak mitral inflow velocity to the point of intersection of the deceleration of flow with the baseline. The product of the "deceleration time" x 0.29 provides the diastolic half-time or the time it takes for the peak pressure gradient to drop by 50%.

Hatle et al[29] proposed an empiric constant of 220 to the Doppler obtained half-time to derive a mitral valve area as shown below:

Mitral Valve Area = 220 / pressure-half time

The Doppler-derived valve area was shown to correlate with valve area obtained by cardiac catheterization and is now universally applied to determine valve area in most echocardiographic laboratories.

However, there are limitations to the Doppler-derived diastolic half-time method for measurement of valve area.[34, 35] The diastolic half-time describes the relative pressure decrease between left atrium and left ventricle and is not only affected by the degree of mitral valve obstruction but also by factors such as initial transmitral driving pressure, left atrial compliance, effective left ventricular compliance. Thus the diastolic haft-time method may he inaccurate when there are significant abnormalities of left atrial compliance (as occurs immediately after valvotomy or other mitral operation or left ventricle compliance (immediately after valvotomy, left ventricular diastolic abnormalities, or severe aortic regurgitation). It may he difficult to measure a diastolic half-time if there is a fast heart rate with fusion of initial and late diastolic peak velocities (E- and A-wave fusion). With concomitant abnormalities of left ventricular diastolic function, there may not be a linear fall in diastolic velocity on the transmitral flow velocity curve and the half-time cannot be measured.

In all cases of mitral stenosis, the calculated valve area by diastolic half-time should be correlated with the clinical presentation and the transmitral gradient. If there is a discrepancy among these parameters, additional information is required. This information may consist of other non-invasive measurements of mitral valve area such as the continuity equation [36], proximal acceleration method [37] or valve area measured by two-dimensional echocardiography.

Mitral Valve Area Calculation by Doppler Echocardiography: Continuity Principle

A mitral valve area may be calculated in selected patients with the continuity principle. [36] The continuity principle is based on the concept that flow remains constant through all heart valves in the absence of valve regurgitation or shunts. Flow through a valve can be measured by Doppler echocardiography from the product of the valve orifice area and time velocity integral of the Doppler flow through the valve. Thus a mitral valve area can be calculated by equating flow through the left ventricular outflow tract with flow through the stenotic mitral valve orifice. Flow through the left ventricular outflow tract is the product of the area of the outflow tract and the time velocity integral of a pulsed-wave Doppler interrogation of the outflow tract. Flow through the mitral valve is the product of the mitral orifice and the time velocity integral of the continuous-wave Doppler mitral velocity curve.

$$LVOT_{area} \times LVOT_{TVI} = MV_{area} \times MV_{TVI}$$

Rearranging this equation provides the mitral valve area as shown in Equation below:

$$\text{Mitral Valve Area} = (LVOT_{area} \times LVOT_{TVI}) / MV_{TVI}$$

Where MVA equals mitral valve area, $LVOT_{area}$ equals left venticular outflow area, $LVOT_{TVI}$ equals time velocity integral of left ventricular outflow tract velocity, and the MV_{TVI} equals time velocity integral of the transmitral velocity profile. Because relative flows are measured on a beat-to-beat basis, irregular rhythms such as atrial fibrillation decrease the accuracy of the technique. In patients with atria fibrillation, an average of 8 to 10 cycles is necessary. If there is differential flow through either the mitral valve or aortic valve (as in mitral regurgitation or aortic regurgitation), the continuity equation cannot be applied (Table 2.3). Because the continuity method is dependent on accurate

measurement of volumetric flow, it should he used only by laboratories with experience in the technique of quantitative Doppler measurement.

Mitral Valve Area by Echocardiography: The Proximal Isovelocity Surface Area Method (PISA)

The proximal isovelocity surface area method may also be used to determine mitral valve area. It is based on calculation of volumetric flow through the mitral valve from color-flow imaging of the convergence of flow proximal to the stenotic valve. The accuracy of this method has been shown in limited studies to be comparable to other noninvasive measures of valve area.[37] This method is tedious, however, and consists of many assumptions about the timing and shape of the area of the proximal convergence. At the present time, it as method is not routinely used even in the high-volume laboratories. As experience with this method increases, it may become a reasonable alternative to estimation of valve area when other methods are considered inaccurate.

Table 2.3 Problems and Pitfalls of Mitral Valve Area Measurement

- **Doppler echocardiography**
  - Half time method problems
    - Abnormal LA compliance
      - After percutaneous balloon mitral valvotomy
      - After MV operation
    - Abnormal LV compliance
      - After percutaneous balloon mitral valvotomy
      - LVH
      - Restriction to filling
    - Aortic regurgitation
  - Continuity method problems
    - Irregular rhythms
    - Differential flow
      - Aortic regurgitation
      - Mitral regurgitation
- **Cardiac catheterization**
  - Gradient problems
  - Use of pulmonary artery wedge pressure
  - Cardiac output problems
    - Thermodilution
      - Tricuspid regurgitation
      - Atria fibrillation
      - Mitral regurgitation
    - Fick method
      - Mitral regurgitation
    - Other
      - Low and high flow states
      - Low and high heart late

LA, left atrium; MV = Mitral valve; LV, left ventricle; LVH, left ventricular hypertrophy; PAWP, pulmonary artery wedge pressure.

Treatment of Mitral Stenosis

Medical Management

Mitral stenosis is a mechanical disorder. Therefore medical therapy can only be expected to ameliorate symptoms. It can neither cause regression of the disease process nor can it delay or prevent progression. Medical management is not required in the symptom-free patient in normal sinus rhythm with mild mitral stenosis. However, because mitral stenosis is most often caused by rheumatic fever, prophylaxis for rheumatic fever is recommended, as is prophylaxis for infective endocarditis.[22, 23] Digoxin may be beneficial in patients in sinus rhythm who have associated right-sided heart failure. Salt reduction and intermittent diuretic therapy is useful if pulmonary vascular congestion is present. In addition, patients with more than a mild degree of mitral stenosis, avoidance of unusual physical stress should be advised.

Treatment of acute onset of rapid atrial fibrillation is aimed at heart rate control and anticoagulation. Patients who have been in atrial fibrillation for longer than 24 to 48 hours without anticoagulation are at greater risk of embolic events after cardioversion. Long-term warfarin anticoagulation is required in all patients with mitral stenosis and atrial fibrillation.

Surgical Intervention

The concept of mitral commissurotomy was first proposed by Brunton in 1902 and a first successful surgical mitral commissurotomy was performed in the 1920s. By the late 1940s, closed surgical commissurotomy was an accepted clinical procedure. With the development of cardiopulmonary bypass in the 1950s, open mitral commissurotomy and replacement of mitral valve became the surgical procedures of choice for the treatment of mitral stenosis.

As with percutaneous mitral balloon valvotomy , the mechanism of improvement in either closed or open surgical commissurotomy is to split open the fused commissures. This results in a decrease in gradient and increase in calculated mitral valve area with improvement in clinical symptoms. Similarly, the extent of hemodynamic and clinical improvement in patients undergoing closed or open surgical commissurotomy depends on the underlying structure of the mitral valve apparatus. It is the patients with pliable non-calcified valve and minimal fusion of the subvalvular apparatus who achieve the best immediate and long-term results.

In the 1950s and 1960s, closed surgical commissurotomy was performed by use of either a transatrial or transventricular approach. Long-term follow-up of these patients showed continued improvement in symptoms with improved mortality rates as compared with a comparable group of patients treated medically.[38] Closed commissurotomy still remains the surgical technique of choice in many developing countries.

However, open commissurotomy is the accepted surgical procedure in most institutions in the United States. In addition, mitral valve replacement is an accepted surgical procedure for patients with severe mitral stenosis who are not candidates for surgical commissurotomy or percutaneous mitral balloon valvotomy .

Percutaneous Mitral Balloon Valvotomy

There have been significant changes in the evaluation and treatment of a patient with mitral stenosis as compared with several decades ago. The cardiac catheterization laboratory in the past provided important hemodynamic information about the severity of obstruction across the mitral valve and its effect on the pulmonary circulation, both at rest and during exercise. Currently, the noninvasive laboratory, with the use of two-dimensional and Doppler echocardiography, has supplanted cardiac catheterization for diagnosis and determination of severity in patients with suspected mitral stenosis. The catheterization laboratory has now assumed a therapeutic role, as percutaneous mitral balloon valvotomy has become an accepted form of therapy for selected patients with mitral stenosis. The ability to split fused commissures from a percutaneous approach has led to recommendations for earlier intervention in patients with mitral stenosis, to prevent the long-term sequelae from long-standing severe inflow obstruction.

Percutaneous mitral balloon valvotomy was first described by Inoue et al. in 1984 [1] and became a clinically approved technique in 1994. This is a catheter-based procedure by which either one or two inflatable balloons are introduced into the left atrial via a transseptal puncture and advanced across the stenotic mitral valve. Once the catheter is in position, the balloon is inflated further, resulting in splitting of the fused mitral commissures.[39] This procedure reduces the transmitral gradient, increases the mitral valve area, and results in significant clinical improvement in selected patients.

There have been major advances in technique and equipment, as well as changes in patient selection over the past decade. Initially, a **double balloon technique** was used by most investigators. This used stiff balloons with the limitation of a single size inflation resulting in problems

with perforation of the left ventricular apex, large atrial septal defects, and severe mitral regurgitation. Currently, the **Inoue balloon** is used by most centers. The Inoue balloon has an hourglass configuration and sequential inflation of a distal, proximal, and then middle portion of the balloon provides stability across the mitral valve during dilation. In addition, sequential increases in inflation balloon size are performed. After each inflation, measurement of valve gradient and mitral regurgitation can be made to determine whether larger balloon inflation sizes are required. The procedure itself is technically challenging and operator dependent, and a steep learning curve is involved. This is supported by a higher success rate and lower complication rate in centers performing more than 100 procedures.[7]

Preprocedural Evaluations

Preprocedural workup includes careful evaluation by history, physical examination, and two-dimensional and Doppler echocardiography. The patients with pliable mitral valves and little subvalvular disease have had the optimal results from the procedure.[8, 40, 41] Several different echocardiographic scores have been proposed to describe the morphologic condition of the mitral valve apparatus. A score by Abascal et al[42] is commonly used, in which four components are evaluated. These consist of the leaflet thickness, leaflet mobility, leaflet calcification, and degree of subvalvular fusion (Table 2.4). Each factor is given a score of 1 to 4, with 1 being least involvement and 4 being most involved. The sum of the four factors is the total mitral valve score, which can ranges from 0 to 16.

Table 2.4 Grading of mitral valve characteristics from the echocardiographic examination [43]

Grade	Mobility	Subvalvular thickening	Thickening	Calcification
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets near normal in thickness (4-5 mm)	A single area of increased echo brightness
2	Leaflet mid and base potions have normal mobility	Thickening of the chordal structures extending up to a one third of the chordal length	Mid-leaflet normal, considerable thickening of margins (5-8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to a distal third of the chords	Thickening extending through the entire leaflet (5-8 mm)	Brightness extending into the mid-portion of the leaflets
4	No or minimal Forward movement or the leaflets in diastole	Extensive thickening And shortening of all Chordal structures extending down to The papillary muscles	Considerable Thickening of all Leaflet tissue (>8-10 mm)	Extensive brightness Throughout much of The leaflet tissue

The total echocardiographic score was derived from an analysis of mitral leaflets mobility, valvular and subvalvular thickening, and calcification which were graded from 1 to 4 according to the above criteria. This scoring grade has been evaluated to predict the acute and long-term outcome of percutaneous balloon valvotomy.[44-46] Patients with score of 8 or less have excellent acute results with a low incidence of complications. Patients with a score greater than 10 have a greater chance of a suboptimal results and higher rate of complications. There is a higher rate of restenosis in patients with the higher preoperative echocardiographic score.

The mechanism of successful balloon valvotomy is splitting open the fused commissures. The appearance of the commissures as assessed from the short-axis transthoracic view is important. In patients with no calcification in the commissures, there is a >95% chance of a successful procedure with an excellent long-term outcome. Alternatively, in patients with calcification in the commissures, there is a higher complication rate and lower event-free survival.[47]

The degree of mitral regurgitation should also be carefully assessed. If severity of mitral regurgitation is 3+ or 4+ on the basis of physical examination and noninvasive studies, percutaneous balloon valvotomy should not be performed. If there is doubt about the severity of regurgitation, a left ventriculogram should be used to assess the severity of regurgitation. Mitral regurgitation can be detected and semiquantitatively graded from left ventriculography. The grading is based on the amount of the regurgitant contrast agent from ventricle into left atrium during ventricular systole according to Sellers' criteria.[48]

Table 2.5 Sellers' Grading of Mitral Regurgitation from Left Ventriculography [48]

1+ Mild: shows a regurgitant jet with minimal staining of the left atrium which clears rapidly.
2+ Moderate: There is a regurgitant jet with moderate opacification of the left atrium which tends to clear rapidly.
3+ Moderately severe: The left atrium is opacified as intensely as the left ventricle and aorta on the late film. The radiopaque medium clears slowly from the left atrium. No jet is seen. The left atrium is usually, although not always, greatly enlarged.
4+ Severe: The left atrium is more densely opacified than the left ventricle or aorta. The left atrium is usually markedly enlarged and the left ventricle dilated. The left atrium remains intensely opacified through the entire series of films.

Results Of Percutaneous Mitral Balloon Valvotomy

The acute complications and immediate and long-term results of percutaneous mitral balloon valvotomy are dependent on multiple factors. These include age, New York Heart Association Functional Class, stenotic severity and pulmonary artery pressure.[8, 45, 49] However, the underlying mitral valve structure is the most important in determining outcome. Patients with calcified, thickened, poorly mobile leaflets with subvalvular disease and calcified commissures have a higher incidence of acute complications and higher rates of restenosis.[47] In contrast, those with suitable mitral valve structure have a high success rate (>90%), low complication rate (<23%), and sustained improvement in 80% to 90% over 3 to 7 years follow-up.[49, 50]

The overall results of percutaneous mitral balloon valvotomy are similar to surgical mitral commissurotomy.[7, 8, 49] The mean valve area usually doubles (from 1.0 cm^2 to 2.0 cm^2) with a 50% to 60% reduction in transmitral gradient. A successful procedure, defined as mitral valve area greater than 1.5 cm^2 in absence of complications, is achieved in 80% to 95% of patients, dependent on the underlying morphologic structure of the mitral apparatus after percutaneous mitral balloon. The 5- to 7-year event free (free of death, repeat valvotomy , or mitral valve replacement) survival rate overall is 50% to 65%. This increases to 80% to 90% in patients with favorable mitral valve structure. More than 90% of patients surviving remain in New York Heart Association Functional Class I or II after percutaneous mitral balloon valvotomy.

Recently, Kang et al[51] reported a randomized trial comparing double balloon vs. Inoue balloon with the 7-year event-free survival. They found no significant difference between the two groups according to the type of balloon used. But the favorable long-term outcome depends on the "success" procedure, define as early post-valvotomy valve area $\geq$ 1.5 cm^2 and mitral regurgitation severity grading $\leq$ 2 (Figure 2.5).

Percutaneous mitral balloon valvotomy has been compared to both open and closed surgical commissurotomy in several randomized trials[2, 3, 52, 53]. There was no significant difference in acute hemodynamic results, complication rate, clinical improvement, or exercise time at 1 to 3 years follow-up. However, these randomized trials evaluated younger patients (10 to 30 years old) with pliable mitral valve leaflets.

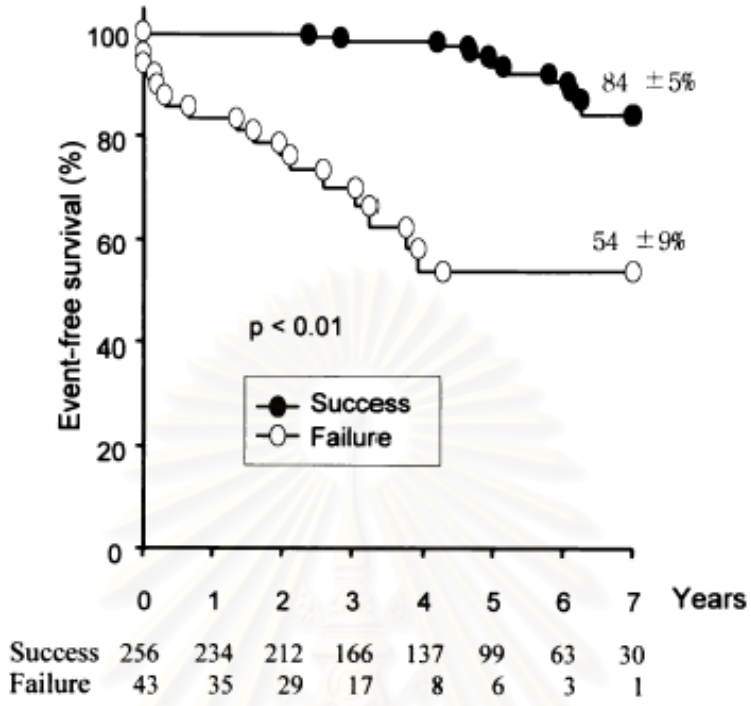


Figure 2.5 Actuarial curves showing the event-free survival rate according to the immediate result after percutaneous mitral valvotomy. Successes and failures were classified according to the immediate results of percutaneous mitral valvotomy. "Success" was defined as post- percutaneous mitral valvotomy mitral vale area $\geq$1.5 cm ^{2} and mitral regurgitation $\leq$ 2, and "Failure" defined as post- percutaneous mitral valvotomy MVA <1.5 cm^2 or mitral regurgitation $\geq$ 3.

Immediate Results after Balloon Mitral Valvotomy

Iung et al[6] reported immediate results of balloon mitral valvotomy and tried to develop a predictive model on a series of 1,514 patients who underwent balloon valvotomy between 1986 and 1995. Mean age of the patients was 45±15 years. Echocardiography showed that 245 patients (16%) had pliable valves and mild chordal thickening (group 1), 886 (59%) had extensive subvalvular disease (group 2), and 383 (25%) had calcified valves (group 3). Percutaneous balloon mitral valvotomy failed in 22 patients; it was performed with a single balloon in 30 patients, a double balloon in 586, and the Inoue balloon in 876. The criteria for stopping the procedure were complete

opening of at least one commissure with a valve area >1 cm^2/m^2 body surface area or >1.5 cm^2 or the appearance or increase of regurgitation >1/4. Good immediate results were defined as a valve area >1.5 cm^2 with mitral regurgitation < Sellers' grade 2 and were obtained in 1348 patients (89%). A logistic model developed from the first 1088 cases identified the following predictors of immediate results: age (P=.004), echocardiographic group (P<.0001), valve area (P<.0001), and effective balloon dilating area (P=.03). Two interactions were significant: age at previous commissurotomy (P=.013) and effective balloon dilating area by initial mitral regurgitation (P=.034). The type of balloon was of borderline significance (P=.09). Then, they validated the model on an independent sample comprising the subsequent 426 procedures. For a threshold of probability of good results of .75, sensitivity was 92%, specificity 25%, and predictive accuracy 87%.

Intermediate-term Survival after Balloon Mitral Valvotomy

Orrange et al[49] reported the intermediate-term survival and event-free survival (7 years) and identified predictors of intermediate-term survival and event-free survival in 132 patients from 1986 through 1994. The double-balloon technique was used in 83 patients, and the Inoue balloon was used in 49. The Actuarial 7-year survival was 95±1%; when mortality after mitral valve replacement is included, 7-year survival was 83±6%. Actuarial 1-, 3-, 5-, and 7-year event-free survival (survival without mitral valve replacement or repeat balloon mitral valvotomy) was 80±4%, 77±4%, 65±6%, and 65±6%. On multivariate analysis, the only two independent predictors (after balloon valvotomy) of 7-year event-free survival were mitral valve area of ≥1.5 versus <1.5 cm^2 (75±7% versus 32±12%) and mean pulmonary artery wedge pressure of ≤ 18 versus >18 mmHg (84±6% versus 38±11%) (*P*<.001 for both). Patients with mitral valve area of 1.5 cm^2 (n=96) could be further subdivided into high- and low-risk subgroups for 7-year event-free survival by two post-valvotomy variables: mean pulmonary artery wedge pressure of ≤ 18 versus >18 mmHg (90±6%

versus 48±14%) (P=.0002) and cardiac index of ≥ 2.5 versus <2.5 litres/min/m^2 (82±8% versus 61±13%) (P=.004). Patients with post-valvotomy whose mitral valve area less than 1.5 cm^2 (n=24) had no additional predictors of event-free survival. Patients who did not undergo mitral valve replacement or repeat balloon valvotomy, 8% were in New York Heart Association functional class III and 92% were in class I or early class II at the last follow-up.

Ballooned Mitral Valvotomy Compare with Surgical Close Commissurotomy and Surgical Open Commissurotomy

Ben Farhat et al[4] conducted a prospective, randomized trial comparing the results of the 3 procedures in 90 patients (30 patients in each group) with severe pliable mitral stenosis. Cardiac catheterization was performed in all patients before and at 6 months after each procedure. All patients had clinical and echocardiographic evaluation initially and throughout the 7-year follow-up period. Gorlin mitral valve area increased much more after balloon valvotomy (from 0.96 ± 06 to 2.26 ± 0.4 cm^2) and open mitral commissurotomy (from 0.96 ± 0.2 to 2.26 ± 0.4 cm^2) than after close mitral commissurotomy (from 0.96 ± 0.2 to 1.6 ± 60.4 cm^2). Residual mitral stenosis (mitral valve area < 1.5 cm^2) was 0% after balloon mitral valvotomy or open mitral commissurotomy and 27% after close mitral commissurotomy. There was no early or late mortality or thromboembolism among the three groups. At 7-year follow-up, echocardiographic mitral valve area was similar and greater after percutaneous balloon mitral valvotomy and open mitral commissurotomy (1.86 ± 0.4 cm^2) than after close mitral commissurotomy (1.36 ± 0.3 cm^2 ; P< 0.001). Restenosis (mitral valve area <1.5 cm^2) rate was 6.6% after percutaneous mitral valvotomy or open mitral commissurotomy versus 37% after close mitral commissurotomy. Residual atrial septal defect was present in 2 patients and severe grade 3 mitral regurgitation was present in 1 patient in the balloon mitral valvotomy group. Eighty-seven percent of patients after percutaneous mitral valvotomy and 90% of patients after open mitral

commissurotomy were in New York Heart Association functional class I versus 33% ($P < 0.0001$) after close mitral commissurotomy. Freedom from reintervention was 90% after percutaneous balloon mitral valvotomy, 93% after open mitral commissurotomy, and 50% after close mitral commissurotomy.

The investigators concluded that, In contrast to surgical close mitral commissurotomy, percutaneous mitral valvotomy and open mitral commissurotomy produce excellent and comparable early hemodynamic improvement and are associated with a lower rate of residual stenosis and restenosis and need for reintervention. However, the good results, lower cost, and elimination of drawbacks of thoracotomy and cardiopulmonary bypass indicate that percutaneous mitral valvotomy should be the treatment of choice for patients with tight pliable rheumatic mitral stenosis.

Complications of Percutaneous Mitral Balloon Valvotomy

The overall mortality rate of percutaneous mitral balloon valvotomy in larger series has ranged from 1% to 2%. However, with increasing experience, a mortality rate of <1% could be achieved.[49, 54]

The most frequent complication of percutaneous mitral balloon valvotomy is an increase in mitral regurgitation. Severe mitral regurgitation necessitating mitral valve replacement during the same hospitalization occurred in 3% of patients in the North America Inoue Balloon Registry. Severe

mitral regurgitation (grade 4) occurred in <3%. One third of patients had a one-grade increase in mitral regurgitation. Overall, two thirds of patients had 1+ or less mitral regurgitation after the procedure.

A residual atrial septal defect has been reported to occur after balloon valvotomy with a frequency range from less than 20% to as high as 87% of patients; depending on the technique used for detection of a left to right shunt. The left-to-right shunt is consequent to the atrial septostomy performed at the time of the procedure. It is more common in those patients with suboptimal relief of the transmitral gradient in whom elevated left atrial pressure persists. Shunt ratios of greater than 1.5:1 are observed in only 3% to 5% of patient, and many defects with a shunt ratio < 1.4:1 disappear a few months after the procedure.

Other complications occur less frequently and include (1) perforation of the left ventricle (0.5% to 4%), (2) complications resulting from transseptal puncture (1%), (3) embolic events (1% to 3%) and (4) myocardial infarction (0.3% to 0.5%). The incidence of these complications has been significantly reduced with the use of pre- or peri-procedural transesophageal echocardiography and the Inoue balloon.

The Percutaneous Mitral Valvotomy with the Metallic Commissurotome

Recently, Cribier et al [9] developed a percutaneous valvotomy device featuring a metallic commissurotome (Figure 2.6) instead of a balloon for opening the mitral valve. The principle of the metallic commissurotome is basically similar to the metallic device (Tubbs dilator) used by surgeons for closed-chest mitral commissurotomy. The main advantage of this device would be the possibility of being reused several times without any loss of performance after proper resterilization, and thus a

decreased procedural cost. Other potential interests might be the improved efficacy of the procedure from mechanical properties of the device, which are aimed at acting principally on the mitral commissures.

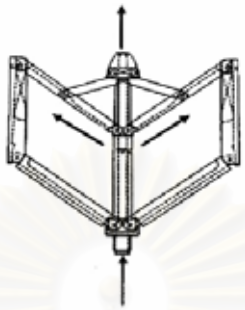


Figure 2.6 Tip of the Overture™ metallic commissurotome

The technique, which is performed under local anesthesia and mild sedation, requires a transseptal antegrade approach. The entry site is the right femoral vein, which has to be punctured 2 cm below the inguinal ligament to avoid hindrance of the dilator. An 8F Mullins catheter is used for the transseptal puncture. A floating balloon catheter is advanced through the sheath and used to cross the mitral valve. The commissurotome is then advanced over the wire, and its distal end is placed across the mitral valve (Figure 2.7 B). At that time, the guidewire is pulled back until the bead is firmly held against the tip of the valvulotome and then securely fastened by screwing the threaded fastener of the pliers. The dilation can then be performed by squeezing the arms of activating pliers (Figure 2.7 C). At least 2 openings of the dilating bars are performed. After dilation, the device is pulled back into the left atrium, with the guidewire in place in the left ventricle. The transvalvular gradient is assessed, the left atrial pressure being measured with the pressure line of the device.

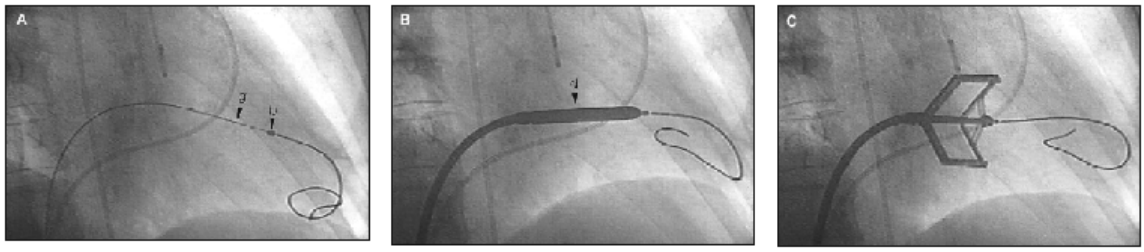


Figure 2.7 Percutaneous mitral valvotomy with the metallic commissurotome.
A, Guidewire (g) is placed in left ventricle after transseptal catheterization. Metallic bead (b) is positioned at midventricle, beyond mitral valve. B, After dilation of septal puncture site, device is pushed over guidewire and metallic dilator (d) positioned across mitral valve. Metallic bead is placed in contact with distal end of dilator. C, Commissurotomy is performed by opening dilator to its maximum extent of 40 mm.

The initial results[9] consisted of 153 patients with a broad spectrum of mitral valve deformities. The procedure was successful in 92% of cases and resulted in a significant increase in mitral valve area, from 0.95 $\pm$ 0.2 to 2.16 $\pm$ 0.4 cm^2. No increase in mitral regurgitation was noted in 80% of cases. Bilateral splitting of the commissures was observed in 87%. Complications were 2 cases of severe mitral regurgitation (1 requiring surgery), 1 pericardial tamponade, and 1 transient cerebrovascular embolic event. In this series, the maximum number of consecutive patients treated with the same device was 35. The authors concluded that the results were encouraging and at least comparable to those of current balloon techniques. Moreover, multiple uses after sterilization should markedly decrease the procedural cost, a major advantage in countries with limited resources and high incidence of mitral stenosis.

Summary

The pathophysiology, clinical, laboratory investigations and treatments of rheumatic mitral stenosis are reviewed. The current treatment of choice in the patients with suitable valve morphology is percutaneous mitral valvotomy. The most commonly used device is the Inoue balloon. However, the high cost and limited reusability are the limitation. The metallic commissurotome recently becomes an attractive choice because of comparable results and low cost, mainly from the ability to repeated resterilization.

The success rate of percutaneous Inoue balloon mitral valvotomy in King Chulalongkorn Hospital is only 35%. The smaller pre-valvotomy mitral valve area, the smaller body habitus, the higher mitral valve score and the reused Inoue balloon are presumed to account for the low rate of success. The metallic commissurotome will be very attractive, apart from the lower cost, if the higher success rate can be achieved with the device.

CHAPTER 3

RESEARCH METHODOLOGY

1. Research Question

1.1. Primary Research Question

Will percutaneous mitral valvotomy with the metallic commissurotome result in 2 times higher success rate compare with the Inoue balloon?

1.2 Secondary Research Questions

1. Will percutaneous mitral valvotomy with the metallic commissurotome result in different mitral valve area compare with the Inoue balloon?

2. Will percutaneous mitral valvotomy with the metallic commissurotome result in different complications compare with the Inoue balloon?

3. Will percutaneous mitral valvotomy with the metallic commissurotome result in different fluoroscopic time and procedure time compare with the Inoue balloon?

4. Will the metallic commissurotome result in different reuse time and cost compare with the Inoue balloon?

2. Research Objectives

2.1 General Objective

To compare the immediate outcome of percutaneous mitral valvotomy using the metallic mitral commissurotome and the Inoue balloon

2.2 Specific Objectives

1. To compare the success rate of mitral valvotomy between the metallic commissurotome and the Inoue balloon.

2. To compare mitral valve area after mitral valvotomy between the metallic commissurotome and the Inoue balloon.

3. To compare the complications of mitral valvotomy between the metallic commissurotome and the Inoue balloon.

4. To compare the fluoroscopic time and procedure time between the metallic commissurotome and the Inoue balloon.

5. To compare the reuse time and cost of the metallic commissurotome and the Inoue balloon.

3. Hypothesis

3.1 Research Hypothesis

Percutaneous mitral valvotomy with the metallic commissurotome will result in 2 times higher success rate than the Inoue balloon.

3.2 Statistical Hypothesis

Null Hypothesis : H_0

The success rate is equal or less than 2 times higher in the metallic commissurotome group compare to the Inoue balloon group

$$H_o: \text{Success rate}_{\text{Metallic commissurotome}} \leq \text{Success rate}_{\text{Inoue}}$$

Alternative Hypothesis : H_A

The success rate is more than 2 times higher in the metallic commissurotome group compare to the Inoue™ balloon group

$$H_A: \text{Success rate}_{\text{Metallic commissurotome}} > 2 \times \text{Success rate}_{\text{Inoue}}$$

4. Conceptual Framework

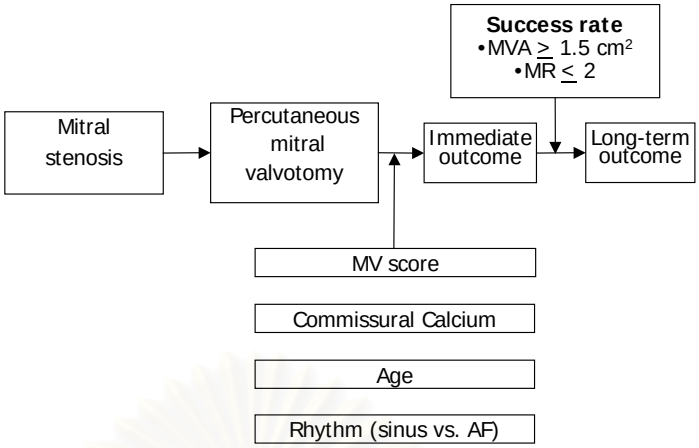


Figure 3.1 Conceptual framework

5. Assumption

Mitral stenosis patients treated with percutaneous mitral valvotomy in King Chulalongkorn Memorial Hospital are not different from the patients treated in other hospital.

6. Key Words

Mitral stenosis | Inoue balloon | Randomized trial

Percutaneous valvotomy | Metallic

7. Operational Definitions

Success : Immediate outcome of percutaneous mitral valvotomy , define as post-valvotomy mitral valve area measured by 2-D echocardiography $\geq$ 1.5 cm^2 and mitral regurgitation severity Sellers' grade $\leq$ 2.[6, 51]

Failure : Immediate outcome of percutaneous mitral valvotomy , define as one of the following

1. Post-valvotomy mitral valve area measured by 2-D echocardiography < 1.5 cm^2
2. Mitral regurgitation severity Sellers' grade[48] > 2
3. Technical failure of the techniques
4. Procedure terminated because of major complications (see **Major Complications** below).

Echocardiographic mitral valve area: Mitral valve area is determined through planimetry of the mitral orifice in a two-dimensional short-axis view early in diastole in all patients before and after any commissurotomy.[28]

Mitral regurgitation: Before and after valvotomy, mitral regurgitation is graded on a scale of 1+ to 4+ with the use of

1. Left ventriculography according to criteria described by Sellers (Table 2.5).[48]
2. If left ventriculogram is not performed or considered technically inadequate, echocardiographic grading of mitral regurgitation according to the jet extension in the left atrium will be used.[55]

Major complications :

1. **Death**
2. **Severe mitral regurgitation**: assessed from left ventricular angiogram[48] or Doppler-echocardiography.[55]
3. **Cardiac tamponade**: hypotension with evidence of accumulating pericardial fluid by fluoroscopy or echocardiography. Pericardial tapping usually relieves the hypotension.

4. **Thromboembolism:** Abrupt onset of neurological deficits that can be anatomically explained by vascular territory.

Procedural time: Time (in minutes) from skin puncture for venous access to withdrawal of the last catheter from the patients.

Fluoroscopic time: Time (in minutes) of fluoroscopy, routinely set to zero at the beginning of the procedure and recorded automatically every time the fluoroscopy is activated.

Reuse time: The number of patients that the Inoue balloon or metallic commissurotome can be used to dilate the mitral valve before it is considered "not reusable". The device will be inspected and considered not reusable by the intervention cardiologist if there is any leakage or distortion of the shape of the balloon (for the Inoue balloon) or improper closure or opening of the metallic commissurotome.

Echocardiographic score: Echocardiographic score described by Abascal et al[42] will be used to assess baseline anatomic features of the mitral valve: a score from 0 (normal) to 4 (severely deformed) was assigned to valvular mobility, thickening and calcification and subvalvular thickening (Table 2.3).

8. **Research Design**

Randomized single-blind controlled experimental trial.

9. **Research Methodology**

9.1. Population

9.1.1. Target and Sample Population

Target Population

Patients who had indication for percutaneous mitral valvotomy for symptomatic mitral stenosis

Sampled Population

Patients who were scheduled to undergo percutaneous mitral valvotomy for symptomatic mitral stenosis in King Chulalongkorn Memorial Hospital

9.1.2 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Patients who were scheduled to undergo percutaneous mitral valvotomy for symptomatic mitral stenosis in King Chulalongkorn Memorial Hospital

2. Age 15 - 80 years old

Exclusion Criteria

1. Mitral regurgitation (before percutaneous mitral valvotomy) Sellers' grade >2

2. Coexistence of aortic valve disease with a valve area < 0.8 cm^2 or aortic regurgitation $\geq$ Sellers' grade 3

3. Other cardiac diseases necessitating open heart surgery

4. Concomitant severe medical illness

5. Coronary stenosis 70% of diameter

6. Pregnancy

7. Unwilling or unable to give the informed consent

9.2. Sample Size Estimation

The primary outcome was the success rate of mitral valvotomy, which was a dichotomous outcome. The sample size was calculated using intercooled STATA 6 immediate command "sampsi" with the following assumptions:

alpha = 0.05 (one-sided)

power = 0.80 (beta = 0.20)

p1 = 0.35

p2 = 0.70

n2/n1 = 1.00

Estimated required sample sizes: n1 = 30, n2 = 30

Total sample size = 60 patients

9.3. Randomization and Allocation Concealment

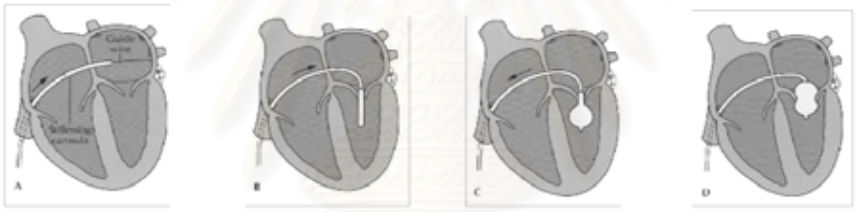
The patients who met the eligibility criteria was randomly divided into two groups by simple randomization using computer-generated random sequences.

The allocation was concealed with the sealed, non-opaque envelope kept by the nurse coordinator at cardiac catheterization laboratory. The allocation was revealed just before the patients underwent the valvotomy.

9.4. Intervention

The Inoue Balloon Commissurotomy Procedure [1, 56]

After administration of local anesthesia, right heart catheterization was performed through the right femoral vein. Interatrial septum was punctured by the Brockenbrough needle, and transseptal catheterization was followed with an 8F Mullins transseptal dilator. After entry into the left atrium, 1,000 units heparin was administered. A pigtail catheter from the femoral artery, usually from the right, was positioned in the left ventricle and simultaneous pressure tracings of the left atrium and the left ventricle were recorded. The balloon was then advanced across the mitral valve and inflated to the predetermined volume (Figure 3.2). Inflation was started at less than the predetermined upper-limit diameter. If the hemodynamic results were suboptimal, the procedure was repeated by increasing the balloon diameter to the predetermined level.



Fugure 3.2 Diagram of percutaneous balloon valvotomy using the Inoue balloon

The Metallic Commissurotomy Procedure [9]

The technique was also performed under local anesthesia and mild sedation. The entry site was the right femoral vein, which was punctured 2 cm below the inguinal ligament to avoid hindrance of the dilator. An 8F Mullins catheter was used for the transseptal puncture. It was recommended that the septal puncture be made 2 cm below the usual site used in the Inoue technique to facilitate the trackability of the device across the valve. Subsequently, after septal puncture, an initial dose of heparin 1000 IU IV was given with an additional dose of 1,000 units after dilation of the atrial septum and confirmation of the absence of pericardial effusion. Both needle and dilator were removed, leaving the Mullins sheath in the left atrium. A floating balloon catheter was advanced through the

sheath and used to cross the mitral valve. The distal end of the balloon catheter was positioned at the apex of the left ventricle, and the sheath was advanced over it, beyond the mitral valve orifice. The balloon catheter was then removed, and the guidewire of the device was advanced through the sheath in the left ventricle, the metallic bead was positioned at mid-ventricle, i.e., clearly beyond the mitral valve. The Mullins sheath was then removed, and a 14F polyethylene dilator was advanced over the wire to enlarge the atrial septum puncture site. The same maneuver was then completed by additional dilation with an 18F dilator, which was also used to enlarge the femoral vein puncture site. The commissurotome was then advanced over the wire, and its distal end was placed across the mitral valve (Figure 3.3B). At that time, the guidewire was pulled back until the bead is firmly held against the tip of the valvulotome and then securely fastened by screwing the threaded fastener of the pliers. The dilation was performed by squeezing the arms of activating pliers (Figure 3.3C). The desired degree of bar opening was obtained by use of the caliper. At least 2 openings of the dilating bars were performed.

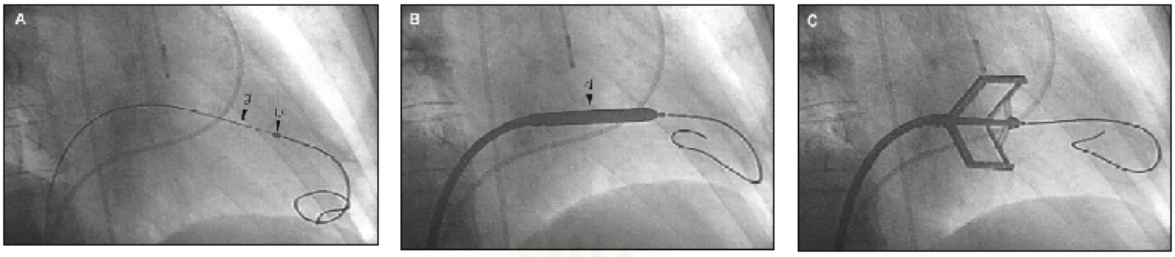


Figure 3.3 Procedure of percutaneous mitral valvotomy with the metallic commissurotome. A, Guidewire (g) is placed in left ventricle after transseptal catheterization. Metallic bead (b) is positioned at midventricle, beyond mitral valve. B, After dilation of septal puncture site, device is pushed over guidewire and metallic dilator (d) positioned across mitral valve. Metallic bead is placed in contact with distal end of dilator. C, Commissurotomy is performed by opening dilator to its maximum extent of 40 mm.

After dilation, the device was pulled back into the left atrium, with the guidewire in place in the left ventricle. The transvalvular gradient was assessed, the left atrial pressure being measured with the pressure line of the device. Whenever available, 2-dimensional echocardiography was performed to assess the quality of commissural splitting and to obtain a preliminary assessment of the mitral valve area. If necessary, an additional opening at a larger size can be made. After valvotomy, a left ventricular angiogram was performed to assess the degree of any subsequent mitral regurgitation.

9.5. Observation and Outcome Measurement

Primary outcome:

Success of the percutaneous mitral valvotomy (post valvotomy mitral valve area $\geq$ 1.5 cm^2 AND mitral regurgitation Sellers' grade $\leq$ 2). According to previous study, this criteria indicated favorable 7-year long-term outcome.[51]

Secondary outcomes :

- Post-valvotomy mitral valve area (cm^2)
- Procedural and fluoroscopic time
- Major complications
- Death
- Mitral regurgitation
- Cardiac tamponade
- Thromboembolism
- Reuse time of the device

9.6. Data Collection

The intervention cardiologist performed the procedure with either the new metallic device or conventional Inoue balloon.

The echocardiography assessing the mitral valve area and other variables post percutaneous mitral valvotomy was performed and collected by a blinded cardiologist one day after the procedure.

Echocardiographic Evaluation

Transthoracic two-dimensional pulsed, color, and continuous-wave Doppler echocardiographic examinations was performed within 1 day before catheterization and 1 day after percutaneous mitral valvotomy.

Echocardiographic mitral valve area

Mitral valve area was determined through planimetry of the mitral orifice in a two-dimensional short-axis view early in diastole in all patients before and after any commissurotomy. The reliability of mitral valve area measurement was presented in Appendix A.

Mitral regurgitation

Before and after valvotomy , mitral regurgitation was graded on a scale of 1+ to 4+ with the use of left ventriculography or Doppler color-flow echocardiography according to the jet extension in the left atrium (when left ventriculography was not available). The reliability of Sellers' grading of mitral regurgitation was presented in Appendix B.

Ehocardiographic score

Ehocardiographic score described by Abascal et al[42] was used to assess baseline anatomic features of the mitral valve: a score from 0 (normal) to 4 (severely deformed) was assigned to valvular mobility, thickening and calcification and subvalvular thickening (Table 2.4).

Transatrial shunting

Left-to-right atrial shunts and the defect size was assessed after the procedure with transthoracic 2-D and Doppler color-flow.

Cardiac catheterization data

Immediately before and after percutaneous mitral valvotomy, the left and right heart pressures and the mean transmitral pressure gradient were measured, and a left ventricular angiogram in the 30° right anterior oblique view was performed using the same amount and delivery rate of contrast to assess the left ventricular function and the presence and severity of any mitral regurgitation.

10. Data Analysis

- Baseline characteristic data were analyzed using descriptive statistics. Continuous data were reported as range and mean $\pm$ standard deviation. Categorical data were reported as number and percent.

- The primary research question was tested by a one-tailed two-sample tests of proportions.
- The secondary outcomes were compared using two-tailed Student t-test for continuous variables and chi-square or Fisher's exact test for categorical variables.
- Statistical significance was set at $p < 0.05$.
- The statistical analysis was carried out by intercooled STATA6.
- If the assumptions for parametric statistical methods were no met, data transformation or nonparametric statistical methods were used as necessary.

11. Ethical Consideration

1. The study was approved by the Institutional Board Review.
2. The patients were given all information about the study, both in the trial and in the alternative intervention, together with adverse effects and potential adverse effects including consequences. And if they agreed to participate, they were asked to sign an informed consent.
3. From the literature review, the metallic commissurotome was a new device with comparable success rate and complication to the conventional Inoue balloon, with the potential benefit of larger post-precedural valve area and lower cost.
4. The patients' withdrawal from the study did not interfere with regular care or benefit.

CHAPTER 4

RESULTS

Baseline Characteristics

The baseline characteristics of the patients were summarized in Table 4.1.

Age

The patients' age ranged from 26 to 78 years. The mean age of the patients was 45.5 years with standard deviation 11.9 years. The mean age in the Inoue group was 49.5 ± 12.2 years, whereas the Metallic commissurotome group was 41.5 ± 10.4 years. The patients in the Inoue group were older than the patients in the Metallic commissurotome group were.

Sex

The 60 enrolled patients were predominantly female (48 female and 12 male). In the Inoue group, 25 (83%) were female and 5 (17%) were male. In the Metallic commissurotome group, 23 (77%) were female and 7 (23%) were male.

Body Weight

The patients' body weight ranged from 35 to 77 kg. The mean body weight of the patients was 54.5 kg with standard deviation 10.3 kg. The mean body weight in the Inoue group was 53.9 ± 10.0 kg, whereas the Metallic commissurotome group was 54.9 ± 10.7 kg.

Table 4.1 The Baseline Characteristics of the Patients.

	Inoue balloon (n = 30)	Metallic commissurotome (n = 30)	p-value
Age	49.5 ± 12.2	41.5 ± 10.4	0.009
Female :male	25 : 5	23:7	0.519
Body surface area	1.51 ± 0.16	1.54 ± 0.17	0.611
History of ARF[1]	-	-	
Previous PMV[2]	3 (10%)	1 (3 %)	0.301
Previous surgical commissurotomy	2 (6%)	1 (3%)	0.554
History of emboli	-	3 (10%)	0.076
NYHA Functional Class			
2	8 (27%)	13 (43%)	0.444
3	20 (67%)	16 (53%)	
4	2 (7%)	1 (3%)	
Rhythm			
Sinus	8 (27%)	14 (48%)	0.071
Atrial fibrillation	22 (73%)	15 (52%)	
Mitral valve score	8.9 ± 1.3	8.4 ± 1.3	0.120
Mobility	2.0 ± 0.0	1.9 ± 0.3	
Thickening	2.1 ± 0.5	2.0 ± 0.6	
Calcification	2.4 ± 0.6	2.1 ± 0.7	
Subvalvular involvement	2.4 ± 0.8	2.4 ± 0.6	
Mitral valve area (cm^2)	0.82 ± 0.20	0.83 ± 0.18	0.740
Mitral regurgitation			
No regurgitation	17 (57 %)	19 (63 %)	0.110
Grade 1	13 (43 %)	8 (27 %)	
Grade 2	-	3 (10 %)	

[1] Acute rheumatic fever

[2] Percutaneous mitral valvotomy

Height

The patients' height ranged from 138 to 178 cm. The mean height of the patients was 156.4 ± 8.5 cm. The mean height in the Inoue group was 155.7 ± 7.6 cm, whereas the Metallic commissurotome group was 157.1 ± 9.3 cm.

Body Surface Area

The patients' body surface area ranged from 1.23 to 1.90 m^2. The mean body surface area of the patients was 1.52 ± 0.16 m^2. The mean body surface area in the Inoue group was 1.51 ± 0.16 m^2, whereas the Metallic commissurotome group was 1.54 ± 0.17 m^2.

History of Acute Rheumatic Fever

No patients reported previous history of acute rheumatic fever.

Previous Percutaneous Mitral Valvotomy

Three of the patients in the Inoue group (10%) and one patient (3%) in the Metallic commissurotome group had previous percutaneous mitral valvotomy.

Previous Surgical Mitral Valvotomy

Two of the patients in the Inoue group (6%) and one patient (3%) in the Metallic commissurotome group had previous percutaneous mitral valvotomy.

History of Thromboembolism

None of the patients in the Inoue group had history of thromboembolism. However, 3 patients in the Metallic commissurotome group had history of cerebral embolism.

New York Heart Association Functional Class

All patients were symptomatic. Most of the patients in both groups were in New York Heart Association Functional Class 3.

Cardiac Rhythm

Thirty seven patients (63%) had atrial fibrillation. In the Inoue group 22 patients (73%) had atrial fibrillation, whereas 15 patients (52%) had atrial fibrillation in the Metallic commissurotome group.

Mitral Valve Score

The mitral valve score is the sum of scores given for four categories, i.e. mobility, thickening of the valve leaflet, calcification and subvalvular involvement.[57] Each categories has the score from 0 to 4 (Table 2.4), the higher the more deformed valve. The total valve score can range from 0 to 16. In this study, the mean mitral valve score in the Inoue balloon group was 8.9 + 1.3, whereas the mitral valve score in the metallic commissurotome group was 8.4 + 1.4, p = 0.12. The frequency of mitral valve scores in each group were shown in Table 4.2.

Table 4.2 Mitral Valve Score in the Inoue Balloon and Metallic Commissurotome Groups.

Mitral valve score	Inoue balloon (n=30)	Metallic commissurotome (n=30)	Total
6	1 (3%)	3 (10%)	4 (7%)
7	1 (3%)	3 (10%)	4 (7%)
8	10 (33%)	10 (33%)	20 (33%)
9	9 (30%)	9 (30%)	18 (30%)
10	6 (20%)	4 (20%)	10 (17%)
11	2 (7%)	0 (0%)	2 (3%)
12	1 (3%)	1 (3%)	2 (3%)
Mean ± SD	8.9 ± 1.3	8.4 ± 1.4	

The mitral valve score was not significantly different between the two groups. The detailed classification of each component of the mitral valve score, i.e. mobility, valvular thickening, calcification and subvalvular involvement were presented in the Table 4.3 - 4.6.

Table 4.3 Mobility Score of the Mitral Valve.

Mobility score	Inoue balloon (n=30)	Metallic commissurotome (n=30)	Total
1	0(0%)	3 (10%)	3 (5%)
2	30 (100%)	27 (90%)	57 (95%)
Mean ± SD	2.0 ± 0.0	1.9 ± 0.3	

Table 4.4 Thickening Score of the Mitral Valve.

Thickening score	Inoue balloon (n=30)	Metallic commissurotome (n=30)	Total
1	2 (7%)	5 (17%)	7 (11%)
2	23 (77%)	20 (57%)	43 (72%)
3	5 (17%)	5 (17%)	10 (17%)
Mean ± SD	2.1 ± 0.5	2.0 ± 0.6	

Table 4.5 Calcification Score of the Mitral Valve.

Calcification score	Inoue balloon (n=30)	Metallic commissurotome (n=30)	Total
1	1 (3	6 (20%)	7 (12%)
2	16 (53%)	17 (57%)	33 (55%)
3	12 (40%)	6 (20%)	18 (30%)
4	1 (3%)	1 (3%)	2 (3%)
Mean ± SD	2.4 ± 0.6	2.1 ± 0.7	

Table 4.6 Subvalvular Score of the Mitral Valve.

Subvalvular involvement score	Inoue balloon (n=30)	Metallic commissurotome (n=30)	Total
1	3 (10%)	0 (0 %)	3 (5%)
2	15 (50%)	19 (63%)	34 (57%)
3	9 (30%)	9 (30%)	18 (30%)
4	3 (10%)	2 (7 %)	5 (8%)
Mean ± SD	2.4 ± 0.8	2.4 ± 0.6	

Mitral Valve Area before Percutaneous Mitral Valvotomy

Fifty-one patients had severe mitral stenosis (mitral valve area equals or less than 1.0 cm^2). The others had moderate mitral stenosis. Mean mitral valve area measured by 2-dimensional echocardiogram was 0.82 ± 0.2 cm^2 in the Inoue group and 0.83 ± 0.18 cm^2 in the Metallic commissurotome group.

Mitral Regurgitation before Percutaneous Mitral Valvotomy

Mitral regurgitation before percutaneous mitral valvotomy was graded semi-quantitatively from left ventricular angiography. The grading of mitral regurgitation in both groups were shown in Table 4.7.

Table 4.7 Grading of Mitral Regurgitation before Percutaneous Mitral Valvotomy.

Grade of Mitral regurgitation	Inoue balloon (n=30)	Metallic commissurotome (n=30)	Total
0 (no MR)	17 (57%)	19 (63%)	36 (60%)
1	13 (43%)	8 (27%)	21 (35%)
2	0 (0%)	3 (10%)	3 (5%)

Hemodynamic Changes Measured by Cardiac Catheterization

The important hemodynamic changes during cardiac catheterization were shown in Table 4.8.

Table 4.8 Hemodynamic Changes Measured by Cardiac Catheterization Immediate Pre And Post-Percutaneous Mitral Valvotomy.

Hemodynamic	Inoue balloon		*p-value*	Metallic commissurotome		*p-value*
	Pre-PMV	Post-PMV	*	Pre-PMV	Post-PMV	*
Pulmonary artery						
Systolic						
Diastolic	60.1 ± 23.3	45.8 ± 12.6	*<0.001*	59.5 ± 19.3	47.2 ± 17.9	*<0.001*
Mean	22.2 ± 8.3	18.9 ± 6.2	*0.016*	26.9 ± 10.5	19.5 ± 8.5	*<0.001*
	38.7 ± 13.3	30.1 ± 8.5	*<0.001*	38.9 ± 12.7	31.5 ± 12.0	*<0.001*
Left atrium						
Mean	27.5 ± 8.3	19.6 ± 6.8	*<0.001*	30.7 ± 7.3	18.1 ± 6.0	*<0.001*

Table 4.8 Hemodynamic Changes Measured by Cardiac Catheterization Immediate Pre And Post-Percutaneous Mitral Valvotomy (continued)

Hemodynamic	Inoue balloon		*p-value*	Metallic commissurotome		*p-value*
	Pre-PMV	Post-PMV	*	Pre-PMV	Post-PMV	*
Diastolic transmitral mean gradient	16.3 ± 6.0	9.0 ± 4.1	*<0.001*	18.9 ± 6.8	7.4 ± 3.9	*<0.001*

* p-value from paired t –test of pre-PMV and post-PMV in the same group.

The Success of Percutaneous Mitral Valvotomy (Primary Research Question)

Success of the procedure was defined as post-valvotomy mitral valve area measured by 2-dimensional echocardiography $\geq$ 1.5 cm^2 and mitral regurgitation severity Sellers' grade $\leq$ 2 without crossover or major complications.

Table 4.9 The Success of Percutaneous Mitral Valvotomy in the Two Randomized Groups.

	Inoue balloon (n=30)	Metallic commissurotome (n=30)	Total
Success	11 (37%)	11 (37%)	22
Not success	19 (63%)	19 (63%)	38
	30 (100%)	30 (100%)	60

The success rate was not different between the two groups. Using one-sided two-sample test of proportion, p-value was 0.5.

Mitral Valve Area Post Percutaneous Mitral Valvotomy (Secondary Research Question)

The mean ± SD of post percutaneous mitral valvotomy mitral valve area in the Inoue balloon group was 1.38 ± 0.28 $cm^{2,}$ in the metallic commissurotome was 1.47 ± 0.33. Although the post-intervention mitral valve area in the metallic commissurotome group was larger, this did not reach statistical significance (p = 0.26).

The mitral valve area increased 0.56 ± 0.30 cm^2 (95% confidence interval 0.45 to 0.67, paired t-test p < 0.0001) with the Inoue balloon and increased 0.64 ± 0.32 cm^2 with the metallic commissurotome (95% confidence interval 0.52 to 0.75, paired t-test p<0.0001). The change in mitral valve area were not significantly different between two groups (p = 0.35).

Mitral Regurgitation Post Percutaneous Mitral Valvotomy (Secondary Research question)

Mitral regurgitation grading after percutaneous mitral valvotomy was listed in Table 4.10 and the change in the degree of mitral regurgitation (after minus before percutaneous mitral valvotomy) in Table 4.11. The degree of mitral regurgitation did not change in most of the patients.

Table 4.10 Grading of Mitral Regurgitation after Percutaneous Mitral Valvotomy.

Mitral regurgitation grade	Inoue balloon (n=30)	Metallic commissurotome (n=30)
0	12 (40%)	12 (40%)
1	9 (30%)	7 (24%)
2	8 (27%)	10 (33%)
3	1 (3%)	1 (3%)

Table 4.11 Changes in Mitral Regurgitation Grading after Percutaneous Mitral Valvotomy.

Mitral regurgitation grade change	Inoue balloon (n=30)	Metallic commissurotome (n=30)
0	18 (60%)	18 (60%)
1	8 (27%)	7 (23%)
2	4 (13%)	5 (17%)

Failure of Percutaneous Mitral Valvotomy and Reasons

The predefined criteria for unsuccessful were: post-valvotomy mitral valve area measured by 2-D echocardiography < 1.5 cm^2 or mitral regurgitation severity Sellers' grade > 2 or technical failure or procedure terminated because of major complications.

Although the unsuccess rate was equal in the two groups. The reasons why the interventions were not a success ones were different between Inoue balloon and metallic commissurotome groups.

Table 4.12 Causes of Percutaneous Mitral Valvotomy Failure.

	Inoue balloon (n=19)	Metallic commissurotome (n=19)	Total
Crossover	0 (0%)	4 (21%)	4
Mitral valve area < 1.5 cm^2	18 (95%)	12 (63%)	30
Mitral regurgitation > grade 2	1 (5%)	1 (5%)	2
Complications:			
Cardiac tamponade	0 (0%)	2 (11%)	2

Major Complications:

Death

There was no death in this study.

Severe Mitral Regurgitation

One patients in each group developed severe mitral regurgitation (p =1.0).

Cardiac Tamponade

In this study, two patients in the metallic commissurotome had cardiac tamponade (p= 0.49). One patient developed tamponade during interatrial septal puncture and could be managed conservatively by pericardiocentesis. This patient later was scheduled for repeated percutaneous mitral commissurotomy with the Inoue balloon successfully. Another patient had tamponade after the guidewire was passed into the left ventricle. The patient was transferred to the operating room because of unstable hemodynamics. At operation, left ventricular perforation was confirmed. The surgeon repaired the small puncture wound and the patient recovered uneventfully. He subsequently underwent percutaneous mitral commissurotomy with the Inoue balloon.

Procedure Time

The procedure time in the Inoue balloon was 57.3 ± 14.7 minutes, whereas the metallic commissurotome was 64.2 ± 15.9 minutes. Percutaneous mitral valvotomy with metallic commissurotome took 6.9 minutes longer than performing the procedure with the Inoue balloon (95% confidence interval -1.1 to 15.0, p 0.09).

Fluoroscopic Time

The fluoroscopic time in the Inoue balloon and the metallic commissurotome were 11.5 ± 6.7 minutes versus 13.4 ± 5.7 minutes. The difference was not statistically significant. Fluoroscopic time was 1.9 minutes longer in the metallic commissurotome group (95% confidence interval -1.3 to 5.3, p 0.24)

Reusability And Cost

The same metallic commissurotome was used in all 30 patients and still usable at the end of the study. The mean time use of the Inoue balloon was 1.3±0.5 (maximum reuse was 2 times). Twenty three Inoue balloons were used for 30 patients in the Inoue group. The cost of the metallic commissurotome at the time of study was 250,000 baht and the cost of the Inoue balloon was 96,000 baht. The cost of the device (Inoue balloon vs. Metallic commissurotome) per success was calculated from

$$\text{Cost of device per success} = \frac{\text{Cost of new device x No. of device used}}{\text{No. of success in each group}}$$

From data in this study, the cost of metallic commissurotome per success was 22,727 baht. On the other hand, the cost of the Inoue balloon per success was 200,727 baht.

CHAPTER 5

DISCUSSION

5.1 Discussion

In this study, percutaneous mitral valvotomy with metallic commissurotome did not have higher success rate than the procedure performed with Inoue balloon. Actually, the success rate of the two devices were the same.

There were some baseline characteristic differences between the two groups. Although the patients were randomized, the baseline differences could occur in the relatively small sample size study. The patients in the Inoue group were older than the patients in the Metallic commissurotome group were (mean difference 7.9 years, 95% CI 2.1 - 13.8). Usually when the patients got older, the stenotic valves became more stiff and calcified. This could result in lower success rate than expected. However, the other baseline parameters including the mitral valve score were not significantly different between the two groups. Therefore the effect of age difference on success rate should not be large.

The patients were predominantly female. This agreed with the prevalence of disease among female gender. Since this was the chronic disease, the patients usually had small body habitus.

Unsuccessful Results

The reasons for unsuccessful result were different. All of the unsuccessful result in the Inoue group were attributed to post-procedural mitral valve area less than 1.5 cm^2. Whereas the causes in the metallic commissurotome group were multiple from crossover, post-procedural mitral valve area less

than 1.5 cm^2, serious complications e.g. cardiac tamponade.

Post-Procedural Mitral Valve Area Less Than 1.5 cm^2

The patients in this study had higher mitral valve score than previously reported in the literature. It was reported that mitral valve score by of equal or less than 8 resulted in a high success rate and fewer complications than the high valve score group. However, if the percutaneous mitral valvotomy were not offered for the patients with high valve score, the patients would have to remain with the disabling symptoms or underwent prosthetic valve replacement. Since prosthetic valves have the risks of its own, e.g. bleeding from anticoagulation, valve dysfunction, infective endocarditis, and thromboembolism etc. We would inform the patients before the procedure of the success rate and complications. Some patients denied having their valve replaced from the beginning.

Crossover

All of the crossover events were in the metallic commissurotome group. The interventionist who performed the procedure switched from the metallic commissurotome to the Inoue balloon because of difficulties passing the guidewire from left atrium ,across the mitral valve, into the left ventricle. This might be the "learning curve" for the new device because the metallic commissurotome did required additional skills in addition to the Inoue balloon.

Major Complications

Severe Mitral Regurgitation

Severe mitral regurgitation (Sellers' grade >2) occurred in 2 patients (1 in each group). Mild mitral regurgitation can be found in 40% of patients after percutaneous mitral valvotomy and is usually produced by commissural splitting [58], the same mechanism as for the increase in mitral valve area [59, 60]. In contrast, severe mitral regurgitation after percutaneous mitral valvotomy is typically caused by leaflet rupture and less frequently by subvalvular apparatus damage [59]. An increase in mitral regurgitation cannot be predicted from the mitral valve score developed by Abascal et al. [42]. Predictive score of severe mitral regurgitation after percutaneous mitral valvotomy with double balloon and Inoue techniques using 2-D echocardiography have been developed by Padial et al. [58, 61] However, this score has not been tested in patients who have percutaneous mitral valvotomy with the metallic commissurotome. The responsible mechanism of severe mitral regurgitation in all of the 4 patients in this study was anterior leaflet rupture. The mean mitral valve score was not different between the patients who developed severe mitral regurgitation and the ones who did not (8.5 ± 1.3 versus 8.7 ± 1.3, $p = 0.79$).

Cardiac Tamponade

Cardiac tamponade is one of the serious complications for percutaneous mitral valvotomy. However, procedure with Inoue balloon did not require passage of the guidewire across mitral valve into the left ventricle. Most, if not all, of cardiac tamponade occur during crossing the interatrial septum. Transesophageal echocardiography monitoring during transseptal puncture decrease the risk of cardiac tamponade. On the contrary, the procedure with metallic commissurotome requires passing the

guidewire into the left ventricle. This poses a risk of left ventricular perforation, hemopericardium and tamponade in addition to the risk of transseptal puncture. If detected early and the perforation is small, tamponade can be managed by pericardiocentesis alone.

5.2 Summary

In this study, percutaneous mitral valvotomy with metallic commissurotome does not have a higher success rate than the procedure with the Inoue balloon. However, the complications from the metallic commissurotome tend to be more serious but may decrease with the operator's experience. The overall cost of the metallic commissurotome is lower because it can be reused many times. Hence, the cost–effectiveness of the percutaneous mitral valvotomy is better with the metallic commissurotome.

5.3 Recommendations for Further Studies

This research focused mainly on the immediate outcome after percutaneous mitral valvotomy. Although the primary outcome was reported to predict long term (7-year) event-free survival.[51] The long-term outcomes in this group of patients should be evaluated.

The success rate in this study is lower than previously reported. The higher mitral valve score seems to be the important factor. If percutaneous mitral valvotomy is to be performed in this group of patients, additional outcomes, e.g. quality of life measurement should be included in the outcome assessment.

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APPENDICES

APPENDIX A

The Reliability of Mitral Valve Area Measurement by Echocardiography

Rationale

In the thesis, the main outcome of the study is success of the immediate results of percutaneous mitral valvotomy. The success is defined as a combination of 1. mitral valve area measured by echocardiography to be $\geq$ 1.5 cm^2 **and** 2. Mitral regurgitation by left ventriculography to be Seller's grade $\leq$ 2. The reliability of these two measurement will be tested. Reliability of measurement of mitral valve area by echocardiography in Appendix A and Seller's grading of mitral regurgitation in Appendix B.

Research Question

To test the reliability for mitral valve area measurement by two-dimensional echocardiography

Research Methodology

Two dimensional echocardiography and Doppler color flow imaging were per-formed in all patients on the day before and 24 h after PMV, using a GE Vingmed System Five echocardiographic machine. All the echocardiographic examinations were recorded in the digital format, using the EchoPac™ archival system, and also in VHS video tape for subsequent review. The morphological features of the mitral valve were categorized as previously described [1], and the total echocardiographic score was obtained by adding the score for each of the following individual morphologic features: leaflet mobility, thickness, calcification, and subvalvular lesions.

Standardization

The echocardiographic measurement package was standardized with the phantom according to the manufacturer's recommendation.

Pretesting

Because the method has been validated, against pathology, during surgery[2]and cardiac catheterization [3-5], only the reliability test was performed. There was only one echocardiologist measuring the valve area, so intra-rater reliability with intraclass correlation (ICC) was the measurement chosen

Data gathering technique

Mitral Valve Area by Two-dimensional Echocardiography

Twenty patients with mitral stenosis admitted for percutaneous balloon valvotomy were included. The echocardiographic loops were obtained and recorded digitally in the EchoPac^{TM} format.

Locating the Mitral Valve

All patients were studied at rest in the left lateral decubitus position with the head elevated. The left ventricular long and short axis two-dimensional echocardiographic examination procedure was performed. The transducer s placed in the third to fifth left intercostal space at the left sternal margin so that the image plane is parallel with the long axis of the left ventricle. Short-axis left ventricular images are obtained by rotating the transducer 90^{o} clockwise so that the viewed plane is perpendicular to the left ventricular long axis. In all patients care was taken to locate the true mitral vale orifice by beginning the short axis sweep at the level of the aorta and the left atrium and slowly bringing the echocardiographic imaging plane toward the left

ventricular apex through the funnel-shaped mitral valve apparatus. Care was taken to examine the mitral valve orifice in early diastole and to clarify the image by altering the transmitting power. The receiver gain was optimized to produce valve echoes that were virtually complete without signal dropout or overlap of neighboring echoes that made orifice detection difficult.[5]

At least 3 cardiac cycles were recorded at parasternal short axis at the level of the smallest mitral vale area during its maximal separation in early diastole. The digital loops were displayed by one doctor in a random selection. The rater reviewed the loops and planimetered the valve area. Three loops were measured per one patient and the average mitral valve area was calculated. One week later, the rater re-measured the mitral valve area in the same manner. The former mitral valve area was compared with the later one.

Statistical Test

The inter-rater reliability of mitral valve area by two-dimensional echocardiography

The data pre-mitral valvotomy were entered into computer with the variable “pre1” and “pre2”. The data post-mitral valvotomy were keyed with the variable name “post1” and “post2”.

Table A1 Raw data for inter-rater reliability of mitral valve area measured by two-dimensional echocardiography

PRE1	PRE2	POST1	POST2
.60	.67	1.30	1.40
.70	.81	1.60	1.55
.80	.90	1.70	1.80
.40	.37	1.75	1.70
.55	.58	1.60	1.60
.62	.60	1.70	1.68
.56	.50	1.80	1.90
.67	.75	1.90	1.88
.89	.99	1.90	1.80
.78	.80	1.45	1.40
.90	1.00	1.60	1.75
.65	.70	1.66	1.60
.76	.85	1.70	1.80
.45	.55	1.80	1.70
.55	.70	1.92	1.78
.78	.80	1.52	1.63
.89	.90	1.64	1.71
.99	1.05	1.43	1.40
.89	.70	1.55	1.63
.78	.65	1.70	1.66

Using the program SPSS version 10, intraclass corelation coefficients were calculated for the pre-valvotomy and post-valvotomy mitral valve area. The outputs from SPSS were demonstrated as follow:

Intraclass Correlation Coefficient for pre-valvotomy MVA

```
Two-Way Mixed Effect Model (Consistency Definition):
People Effect Random, Measure Effect Fixed
Single Measure Intraclass Correlation =    .8739
    95.00% C.I.:            Lower =    .7095          Upper =    .9481
 F =  14.8665   DF = (19,19.0)   Sig. = .0000  (Test Value = .0000)

Reliability Coefficients     2 items
Alpha =   .9327           Standardized item alpha =   .9346
```

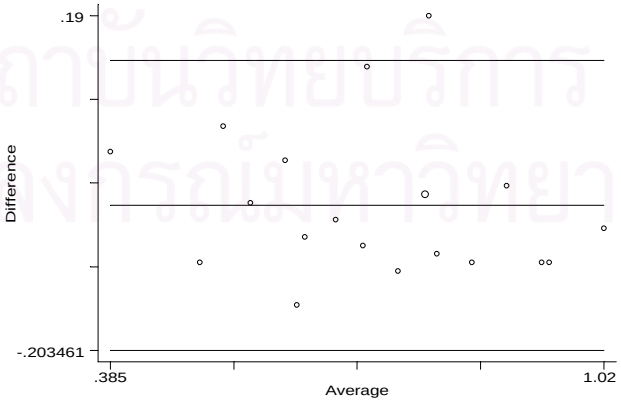
Intraclass Correlation Coefficient Post-valvotomy Mitral Valve Area

```
Intraclass Correlation Coefficient


Two-Way Mixed Effect Model (Consistency Definition):

People Effect Random, Measure Effect Fixed

Single Measure Intraclass Correlation =    .8495

    95.00% C.I.:            Lower =    .6589          Upper =    .9376

 F =  12.2853   DF = (19,19.0)   Sig. = .0000  (Test Value = .0000)


Reliability Coefficients

Alpha =   .8978        Standardized item alpha =   .9020
```

In addition, using stata6 program, the command “baplot” was used to generate Bland and Altman Plot and calculate the mean difference with 95% confidence interval and limits of agreement as follow:

Bland and Altman Plot for Mitral Valve Area Pre-percutneous Mitral Valvotomy

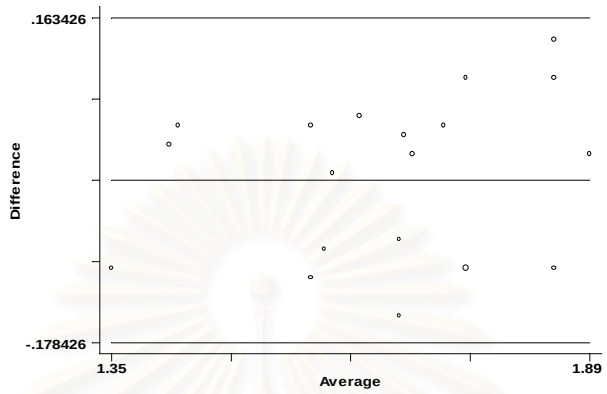
```
. baplot pre1 pre2
```




```
Bland-Altman comparison of pre1 and pre2
Limits of agreement (Reference Range for difference): -0.203 to  0.137
Mean difference: -0.033 (CI -0.073 to  0.007)
Range :  0.385 to  1.020
Pitman's Test of difference in variance: r = -0.179, n = 20, p = 0.465
```

Bland and Altman Plot for Mitral Valve Area Post-percutneous Mitral Valvotomy

```
. baplot post1 post2
```




```
Bland-Altman comparison of post1 and post2
Limits of agreement (Reference Range for difference): -0.178 to  0.163
Mean difference: -0.007 (CI -0.047 to  0.032)
Range :  1.350 to  1.890
Pitman's Test of difference in variance: r =  0.185, n = 20, p = 0.434
```

Agreement of "Success" or "Failure" by Mitral Valve Area

When the continuous data were recoded into dichotomous variable of "success" or "failure" using the cut point of equal or more than 1.5 $cm^{2.}$ The kappa is 1.0.

Interpretation

The results of reliability testing of mitral valve area measurement by two-dimensional showed good agreement. When using the data were recoded as "success" or "failure" using the criteria mentioned above, the agreement for both measurements were 1.0 each.

Conclusion

Mitral valve area measurement by two-dimensional echocardiography were reliable. The measurements can be used with confidence to determine the success rate of percutaneous mitral valvotomy.

References

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4. Smith MD, Handshoe R, Handshoe S, Kwan OL, DeMaria AN. Comparative accuracy of two-dimensional echocardiography and Doppler pressure half-time methods in assessing severity of mitral stenosis in patients with and without prior commissurotomy. **Circulation** 1986; 73:100-7.

5. Martin RP, Rakowski H, Kleiman JH, Beaver W, London E, Popp RL. Reliability and reproducibility of the two dimensional echocardiographic measurement of the stenotic mitral valve orifice area. **Am J Cardiol** 1979; 43:560-8.

APPENDIX B

The Reliability of Sellers' Grading of Mitral Regurgitation

Rationale

In the thesis, the main outcome of the study is success of the immediate results of percutaneous mitral valvotomy. The success is defined as a combination of 1. Mitral valve area measured by echocardiography to be $\geq$ 1.5 cm^2 **and** 2. Mitral regurgitation by left ventriculography to be Sellers' grade $\leq$ 2. The reliability of these two measurements will be tested. Reliability of measurement of mitral valve area by echocardiography in Appendix A and Sellers' grading of mitral regurgitation in Appendix B.

Research Question

To test the reliability for grading of mitral regurgitation from left ventriculography using Sellers' criteria

Research Methodology

Mitral regurgitation is detected and semi-quantitatively graded from left ventriculography. The grading is based on the amount of the regurgitant contrast agent from ventricle into left atrium during ventricular systole

The mitral regurgitation severity is graded by Sellers' criteria[1] (Table B1). The inter-rater and intra-rater agreement with the weighted kappa statistics will be performed to assess reliability.

Table B1 Sellers' Grading of mitral regurgitation from left ventriculography [1]

1+ Mild: shows a regurgitant jet with minimal staining of the left atriumwhich clears rapidly.
2+ Moderate: There is a regurgitant jet with moderate opacification of the left atrium which tends to clear rapidly.
3+ Moderately severe: The left atrium is opacified as intensely as the left ventricle and aorta on the late film. The radiopaque medium clears slowly from the left atrium. No jet is seen. The left atrium is usually, although not always, greatly enlarged.
4+ Severe: The left atrium is more densely opacified than the left ventricle or aorta. The left atrium is usually markedly enlarged and the left ventricle dilated. The left atrium remains intensely opacified through the entire series of films.

Data gathering technique

During the procedure of percutaneous mitral valvotomy, left ventriculogram is performed routinely pre-an post- valvotomy. The ventriculogram is performed in the standard manners in the 30^{o} right anterior oblique view. In our laboratory, cine-angiogram is recorded in a digital format in a CD-ROM for each patient. Twenty CD-ROM were selected by one cardiologist to obtain the varying degrees of mitral regurgitation (no necessarily from the patient undergoing mitral valvotomy).

1. Two cardiologists reviewed the same left ventriculogram and gave each own grading. The data were used for inter-rater reliability.
2. One week later, the two cardiologists looked at the left ventriculogram presented in different order and grade the severity of mitral regurgitation. The second severity grading was compare with the previous one for each cardiologist for intra-rater reliability.

Statistical Method

The weighted kappa statistics for inter-rater agreement of severity of mitral regurgitation was calculated using the Stata "kap" command.

Inter-rater agreement between rater 1 and rater 2

```
. kap  rater1 rater2, tab wgt(w)
           |                rater2
    rater1 |         1          2          3          4 |     Total
-----------+--------------------------------------------+----------
         1 |         7          2          0          0 |         9
         2 |         0          4          0          0 |         4
         3 |         0          0          3          2 |         5
         4 |         0          0          0          2 |         2
-----------+--------------------------------------------+----------
     Total |         7          6          3          4 |        20
Expected
Agreement   Agreement     Kappa   Std. Err.   Z        Pr>Z
-------------------------------------------------------------
  93.33%      60.00%     0.8333     0.1600    5.21     0.0000
```

The weighted kappa statistics for inter-rater agreement of severity of mitral regurgitation equals 0.83. This reaches statistical significance at p-value < 0.001. The kappa denotes almost perfect agreement.

Then the weighted kappa of rater 1 and rater 2 were calculated, respectively. The kappa also showed good intra-rater agreement for both raters.

Weighted Kappa for rater 1

```
. kap  rater1 rater12, tab wgt(w)
           |                   rater12
    rater1 |         1          2          3          4 |     Total
-----------+--------------------------------------------+----------
         1 |         7          2          0          0 |         9
         2 |         1          3          0          0 |         4
         3 |         0          0          5          0 |         5
         4 |         0          0          1          1 |         2
-----------+--------------------------------------------+----------
     Total |         8          5          6          1 |        20

             Expected
Agreement    Agreement      Kappa   Std. Err.          Z        Pr>Z
------------------------------------------------------------------
  93.33%       63.83%      0.8157     0.1677        4.86      0.0000
```

Weighted Kappa for rater 2

```
. kap  rater2 rater22, tab wgt(w)

           |                   rater22
    rater2 |         1          2          3          4 |     Total
-----------+--------------------------------------------+----------
         1 |         6          1          0          0 |         7
         2 |         2          4          0          0 |         6
         3 |         0          0          3          0 |         3
         4 |         0          0          1          3 |         4
-----------+--------------------------------------------+----------
     Total |         8          5          4          3 |        20

             Expected
Agreement    Agreement      Kappa   Std. Err.          Z        Pr>Z
------------------------------------------------------------------
  93.33%       59.50%      0.8354     0.1625        5.14      0.0000
```

Agreement of "Success" or "Failure" by Mitral Regurgitation

When the continuous data were recoded into dichotomous variable of "success" or "failure" using the cut point of equal or less than grade 2 as success. The kappa is 1.0.

Interpretation

The results of reliability testing of severity of mitral regurgitation measurement by left ventriculography showed good agreement. When the data were recoded as "success" or "failure" using the criteria mentioned above, the agreement for the measurements were 1.0.

Conclusion

Mitral regurgitation severity grading from left ventriculography, using Sellers' criteria is reliable. The measurements can be used with confidence to determine the success rate of percutaneous mitral valvotomy.

References

1. Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardioangiography in acquired heart disease. **Am J Cardiol** 1964; 14:437-47.

APPENDIX C

Patient Information Sheet
&
Consent Form

ข้อมูลที่ผู้ป่วยควรทราบ (Patients Information Sheet)

ชื่อโครงการวิจัย ประสิทธิผลของการขยายลิ้นไมตรัลตีบด้วยการสวนหัวใจผ่านหลอดเลือดดำ: การศึกษาเปรียบเทียบระหว่างบอลลูนชนิดอินุเยกับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ

สถานที่ทำการวิจัย คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

ผู้ทำการวิจัย แพทย์หญิงสมนพร บุณยะรัตเวช สองเมือง

อาจารย์ที่ปรึกษา ศาสตราจารย์ นายแพทย์กัมมันต์ พันธุมจินดา

ข้อมูลทั่วไป

ลิ้นไมตรัลตีบเป็นผลแทรกซ้อนระยะยาวของโรคไข้รูห์มาติก ทำให้เกิดอาหารเหนื่อยง่าย การรักษาที่เป็นมาตรฐานคือการขยายลิ้นไมตรัลตีบด้วยการสวนหัวใจผ่านหลอดเลือดดำ อุปกรณ์ที่นิยมใช้อยู่ในปัจจุบันคือบอลลูนชนิดอินุเย โดยมีเครื่องมือใหม่คืออุปกรณ์ขยายลิ้นหัวใจแบบโลหะ ซึ่งมีราคาแพงกว่า แต่มีข้อดีคือสามารถขยายลิ้นได้กว้างกว่า และสามารถนำมาใช้ซ้ำได้หลายครั้งกว่าบอลลูน

ข้อมูลของโครงการ

การศึกษาวิจัยนี้เป็นการศึกษาประสิทธิผลของการขยายลิ้นไมตรัลตีบด้วยการสวนหัวใจผ่านหลอดเลือดดำ โดยเปรียบเทียบความสำเร็จของการขยายลิ้นไมตรัลตีบด้วยบอลลูนชนิดอินุเยกับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ โดยกลุ่มตัวอย่างคือผู้ป่วยลิ้นหัวใจไมตรัลตีบที่จำเป็นจะต้องได้รับการรักษาด้วยการขยายลิ้นหัวใจ จำนวน 60 ราย ผู้ป่วยจะได้รับการสุ่มให้ได้รับการขยายลิ้นไมตรัลตีบด้วยเครื่องมืออย่างใดอย่างหนึ่ง โดยขั้นตอนส่วนใหญ่ในทั้งสองกลุ่มจะไม่แตกต่างกัน

การวัดประสิทธิผลของการขยายลิ้นไมตรัลตีบ ใช้การตรวจคลื่นเสียงสะท้อนหัวใจ โดยวัดผลหนึ่งวันหลังวันขยายลิ้นหัวใจที่ตีบ แล้วเปรียบเทียบความสำเร็จของการขยายลิ้นหัวใจ ระหว่างกลุ่มที่ได้รับการขยายลิ้นหัวใจด้วยบอลลูน กับ กลุ่มที่ได้รับการขยายลิ้นหัวใจด้วยอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ

ประโยชน์ของการทำวิจัย

ข้อมูลที่ได้จากการวิจัยจะช่วยให้แพทย์สามารถเลือกเครื่องมือในการขยายลิ้นหัวใจไมตรัลตีบได้เหมาะสม

ความไม่สะดวกที่อาจจะเกิดจากการศึกษาวิจัย

เนื่องจากขั้นตอนส่วนใหญ่ในผู้ป่วยสองกลุ่มจะไม่แตกต่างกัน และไม่แตกต่างไปจากขั้นตอนตามปรกติของการขยายลิ้นหัวใจ ดังนั้นไม่คาดว่าจะเกิดความไม่สะดวกที่อาจจะเกิดจากการศึกษาวิจัย

ท่านจำเป็นต้องเข้าร่วมในการศึกษาวิจัยนี้หรือไม่

การเข้าร่วมในการศึกษาวิจัยนี้เป็นไปโดยความสมัครใจ แพทย์มีหน้าที่ต้องให้การดูแลรักษาผู้ป่วยอย่างดีที่สุด ไม่ว่าท่านจะตัดสินใจเข้าร่วมโครงการนี้หรือไม่

แพทย์ที่ท่านสามารถติดต่อได้

ท่านสามารถสอบถามรายละเอียดเพิ่มเติมได้จาก อาจารย์ แพทย์หญิงสมนพร บุณยะรัตเวช ใบประกอบวิชาชีพเวชกรรม เลขที่ 13185 หมายเลขโทรศัพท์ที่ติดต่อได้ 256-4291, 256-4184

แบบยินยอมเข้าร่วมโครงการวิจัย

วันที่ .....

ชื่อโครงการวิจัย ประสิทธิผลของการขยายลิ้นไมตรัลตีบด้วยการสวนหัวใจผ่านหลอดเลือดดำ: การศึกษาเปรียบเทียบระหว่างบอลลูนชนิดอินุเยกับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ

ผู้ทำการวิจัย อาจารย์ แพทย์หญิงสมนพร บุณยะรัตเวช ใบประกอบวิชาชีพเวชกรรมเลขที่ 13185 หมายเลขโทรศัพท์ที่ติดต่อได้ 256-4291, 256-4184

วัตถุประสงค์ เพื่อเปรียบเทียบประสิทธิผลของการขยายลิ้นไมตรัลตีบด้วยการสวนหัวใจผ่านหลอดเลือดดำ โดยเปรียบเทียบความสำเร็จของการขยายลิ้นไมตรัลตีบด้วยบอลลูนชนิดอินุเยกับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ

รายละเอียดที่จะปฏิบัติต่อผู้สมัคร

ผู้ที่เข้าร่วมวิจัยคือผู้ป่วยลิ้นหัวใจไมตรัลตีบที่จำเป็นจะต้องได้รับการรักษาด้วยการขยายลิ้นหัวใจ ผู้เข้าร่วมวิจัยจะได้รับการสุ่มให้ได้รับการขยายลิ้นไมตรัลตีบด้วยเครื่องมืออย่างใดอย่างหนึ่ง ระหว่าง บอลลูนชนิดอินุเย หรือ อุปกรณ์ขยายลิ้นหัวใจแบบโลหะ โดยวัดผลหนึ่งวันหลังวันขยายลิ้นหัวใจที่ตีบโดยการตรวจคลื่นเสียงสะท้อนหัวใจ แล้วเปรียบเทียบผลการขยายลิ้นหัวใจระหว่างกลุ่มที่ได้รับการขยายลิ้นหัวใจด้วยบอลลูน กับ กลุ่มที่ได้รับการขยายลิ้นหัวใจด้วยอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ

ประโยชน์และผลข้างเคียงที่จะเกิดแก่ผู้สมัครเข้าร่วมวิจัย

สิ่งที่ผู้เข้าร่วมวิจัยจะได้รับนอกเหนือจากการรักษาด้วยวิธีมาตรฐาน คือได้รับการยกเว้นไม่เก็บค่าตรวจคลื่นเสียงสะท้อนหัวใจในวันรุ่งขึ้นหลังจากการขยายลิ้นหัวใจ และไม่ต้องเสียค่าใช้จ่ายเพิ่มขึ้นในกลุ่มที่ได้รับการขยายลิ้นหัวใจด้วยอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ ส่วนภาวะแทรกซ้อนที่เกิดจากการขยายลิ้นหัวใจด้วยบอลลูนชนิดอินุเยกับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะที่มีรายงานการศึกษาจากต่างประเทศ ไม่มีความแตกต่างกัน

การรับฟังการชี้แจง

ข้าพเจ้า (นาย/ นาง/ นางสาว) .....นามสกุล ..... อายุ ..... ปี

ที่อยู่ .....โทรศัพท์ .....

ได้รับทราบรายละเอียดของโครงการวิจัยเรื่อง ประสิทธิผลของการขยายลิ้นไมตรัลตีบด้วยการสวนหัวใจผ่านหลอดเลือดดำ: การศึกษาเปรียบเทียบระหว่างบอลลูนชนิดอินุเยกับอุปกรณ์ขยายลิ้นหัวใจแบบโลหะ และข้าพเจ้าเข้าใจวัตถุประสงค์ของการวิจัย วิธีการ ประโยชน์ และผลข้างเคียงอันอาจเกิดต่อตัวข้าพเจ้าเองทุกประการ

ข้าพเจ้ามีสิทธิ์ที่จะงดเข้าร่วมโครงการวิจัยโดยมิต้องแจ้งให้ทราบล่วงหน้า และการงดเข้าร่วมโครงการนี้จะไม่มีผลกระทบต่อการให้บริการ หรือการรักษาที่ข้าพเจ้าจะได้รับแต่ประการใด

ข้าพเจ้าได้รับทราบจากผู้วิจัยว่าจะไม่เปิดเผยข้อมูลหรือผลการวิจัยของข้พเจ้าเป็นรายบุคคลต่อสาธารณชน และใช้ข้อมูลที่ได้เพื่อเป็นประโยชน์ทางการแพทย์ การเปิดเผยข้อมูลเกี่ยวกับข้าพเจ้าต่อหน่วยงานต่างๆกระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการหรือกฎหมายเท่านั้น ซึ่งในกรณีดังกล่าวข้าพเจ้าจะไม่เรียกร้องค่าเสียหายใดๆทั้งสิ้น

ข้าพเจ้าได้รับทราบและได้ซักถามผู้วิจัยจนหมดข้อสงสัยโดยตลอดและยินดีเข้าร่วมวิจัย จึงได้ลงลายมือไว้เป็นหลักฐานต่อหน้าพยาน

ลงนาม ..... ผู้ยินยอม

( )

...../...../.....

ลงนาม ..... ผู้วิจัย

( )

...../...../.....

ลงนาม ..... พยาน

( )

...../...../.....

APPENDIX D

Case Record Form

Case Number

Case Record Form

Effectiveness Of Transvenous Mitral Valvotomy:

A Randomized Trial Comparing Balloon And Metallic Commissurotome

INCLUSION AND EXCLUSION CHECKLIST

INCLUSION CHECKLIST

		YES	NO
1.	Is the patient undergoing percutaneous mitral valvotomy for symptomatic mitral stenosis in King Chulalongkorn Memorial Hospital?	☐	☐
2.	Is the patient 15 - 70 years old?	☐	☐

EXCLUSION CHECKLIST

		YES	NO
1.	Does the patient have mitral regurgitation (before percutaneous mitral valvotomy) Sellers' grade >2?	☐	☐
2.	Does the patient have coexisting aortic valve disease with a valve area < 0.8 cm^2 or aortic regurgitation $\geq$ Sellers' grade 3?	☐	☐
3.	Does the patient have other cardiac diseases necessitating open heart surgery?	☐	☐
4.	Does the patient have concomitant severe medical illness?	☐	☐
5.	Does the patient have coronary stenosis 70% of diameter?	☐	☐
6.	Is the patient pregnant?	☐	☐
7.	Is the patient willing and able to give the informed consent?	☐	☐

BASELINE ASSESSMENT

1	Date of assessment (dd-mm-20yy)	__ __ /__ __ / 20 __ __	*dateas*
2	Age (years)	__ __	*age*
3	Gender (1 = male, 2 = female)	__	*gender*
4	Body weight (kg)	__ __	*bw*
5	Height (cm)	__ __ __	*ht*
6	Body surface area (m2)	__ . __ __	*bsa*
7	History of rheumatic fever (0 = no, 1 = yes)	__	*hxrf*
	If yes, specify at what age (yrs)	__ __	
8	Previous PMV (0 = no, 1 = yes)	__	*ppmv*
	If yes, date (dd-mm-20yy)	__ __ / __ __/__ __ __ __	
9	Previous surgical commissurotomy (0 = no, 1	__	*psmv*
	= yes) If yes, date (dd-mm-20yy)	__ __ / __ __/__ __ __ __	
10	Previous emboli (0 = no, 1 = yes)	__	*emboli*
	If yes, to where (1 = brain, 2= extremities, 3=other, specify ……..)		
11	NYHA functional class(1,2,3,4)	__	*prefc*
	Physical examination		
	Lateral shift of apical impulse (0 = no, 1 = yes)	__	*shift*
	RV heaving (0 = no, 1 = yes)	__	*rvheave*
	Lound P_2 (0 = no, 1 = yes)	__	*loundp*
	Diastolic rumbing murmur grade (0 to 6)	__	*drmgr*
	Mitral regurgitation murmur grade (0 to 6)	__	*mrmur*
	Tricuspid regurgitation murmur grade (0 to 6)	__	*trmur*

BASELINE ASSESSMENT (2)
ECG and Chest X-rays

ECG

Rhythm (1=sinus, 2 atrial fibrillaiton, 3 = others, specify _____)	__	*rhythm*
LA enlargement (0 = no, 1 = yes)	__	*ecglae*
RA enlargement (0 = no, 1 = yes)	__	*ecgrae*
RV hypertrophy (0 = no, 1 = yes)	__	*ecgrvh*
LV hypertrophy (0 = no, 1 = by voltage, 2 = with strain pattern)	__	*ecglvh*

Chest X-rays

Cardiomegaly (0 = no, 1 = yes)	__	*cxr*
LA enlargement (0 = no, 1 = yes)	__	*cxrla*
Pulmonary venous hypertension (0 = no, 1 = yes)	__	*cxrpvht*
Pulmonary arterial hypertension (0 = no, 1 = yes)	__	*cxrpaht*

BASELINE ASSESSMENT (3)
Echocardiography

Mitral valve score

Mobility	1 Highly mobile valve with only leaflet tips restricted	2 Leaflet mid and base potions have normal mobility	3 Valve continues to move forward in diastole, mainly from the base	4 No or minimal forward movement or the leaflets in diastole	*mobi*
Thickening	1 Leaflets near normal in thickness (4-5 mm)	2 Mid-leaflet normal, considerable thickening of margins (5-8 mm)	3 Thickening extending through the entire leaflet (5-8 mm)	4 Considerable thickening of all leaflet tissue (> 8–10 mm)	*thic*
Calcification	1 A single area of increased echo brightness	2 Scattered areas of brightness confined to leaflet margins	3 Brightness extending into the mid-portion of the leaflets	4 Extensive brightness throughout much of the leaflet tissue	*calc*
Subvalvular Thickening	1 Minimal thickening just below the mitral leaflets	2 Thickening of the chordal structures extending up to a one third of the chordal length	3 Thickening extending to a distal third of the chords	4 Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	*subv*
TOTAL	=				*sctotal*

Mitral valve area-planimetry (cm^2)	__ . __ __	*premva*
Doppler mean gradient (mmHg)	__ __ . __	*prempg*
MVA by Pressure-half time (cm^2)	__ . __ __	*premvapht*
Mitral regurgitation grade (0,1,2,3,4)	__	*preechomr*
LV end-diastolic diameter(mm)	__ __	*prelvedd*
LV end systolic diameter(mm)	__ __	*prelvesd*
LV ejection fraction	0. __ __	*prelvef*
LA diameter (mm)	__ __ __	*prelad*
RV diameter (mm)	__ __	*prervd*
Tricuspid regurgitaion severity (0,1,2,3,4)	__	*pretrgr*
Tricuspid regurgitaion vel.(m/sec)	__ . __	*pretrvel*

POST-PMV RESULTS

Date of echocardiogram (dd-mm-20yy)	__ __ /__ __ / 20 __ __	*dechopost*
Mitral valve area-planimetry (cm2)	__ . __ __	*pomva*
Doppler mean gradient (mmHg)	__ __ . __	*pompg*
Mitral regurgitation grade (0,1,2,3,4)	__	*poechomr*
LV end diastolic diameter(mm)	__ __	*polvedd*
LV end systolic diameter(mm)	__ __	*polvesd*
LV ejection fraction	0. __ __	*polvef*
LA diameter (mm)	__ __ __	*polad*
RV diameter (mm)	__ __	*porvd*
Tricuspid regurgitaion severity (0,1,2,3,4)	__	*pretrgr*
Tricuspid regurgitaion vel.(m/sec)	__ . __	*potrvel*
Atrial septal defect from TTE (0=no, 1= yes)	__	*poasd*
ASD diameter (mm)	__ __ __	*poasdsi*

Success (0=no, 1=yes) __ *success*
Failure (0=no, 1=yes) __ *failure*
Crossover (0=no, 1=yes) __ *crossov*
Cause of failure __ *clasfail*

1. technical, IAS puncture failure
2. technical, failure to cross MV with both
3. technical, failure to cross MV crossover
4. PMV performed, post-PMV MVA < 1.5 cm^2
5. PMV performed, post-PMV MR > grade 2
6. PMV performed, post-PMV MVA < 1.5 cm^2 and MR > grade 2
7. Precedure terminated because of complications
8. Others, if yes specify _____

Complications(o=no, 1=yes) *compli*

1. Tamponade from IAS puncture	__	*tamp_ias*
2. Tamponade from LV perforation	__	*tamp_lv*
3. Severe MR	__	*severemr*
4. Thromboembolism	__	*emboli*
5. Death	__	*death*
6. Others, if yes specify	__	
	,_____	
Device used (1=Inoue, 2 Metalllic)	__	*device*

==To be entered at the end of study==

END OF TRIAL/STUDY FORM

1. Does the patient Complete study or not (0 =no, 1= yes) ____

2. Date of end of study (DD-MM-YYYY) _ _ - _ _ - 20 _ _

3. Reason of premature discontinuation, specify …….
   ……..
   …….

VITAE

Smonporn Boonyaratavej Songmuang was born on February 4, 1963 in Bangkok Thailand. She graduated *summa cum laude* from the Faculty of Medicine, Chulalongkorn University in 1986. During 1986-1990, She worked at Department of Internal Medicine, Faculty of Medicine, Chiang Mai University and obtained a Thai Board of Internal Medicine in 1990. After that, she completed her cardiovascular fellowship at King Chulalongkorn Memorial Hospital and was certified Thai Board of Cardiology in 1992. She has been working as an instructor at the Division of Cardiology, Department of Medicine, Chulalongkorn University since 1996. In 2000, she was funded by the Ministry of University and admitted in the Master of Science (Health Development) program organized by THAI CERTC in conjunction with Faculty of Medicine, Chulalongkorn University.

She spent two years (1994-1996) as a clinical research fellow at the Cardiovascular Ultrasound Imaging and Hemodynamic Laboratory or "Echo Lab" at the Mayo Clinic, Rochester, Minnesota, USA. She passed the American Society of Echocardiography Examination for Special Competency in Echocardiography in 1996 and received a Comprehensive Certification in Adult Echocardiography from National Board of Echocardiography, USA in 2002.

Her areas of interest are noninvasive cardiac investigations especially echocardiography and valvular heart disease.