THE OUTCOME OF PATIENTS UNDERGOING SIMULTANEOUS TRICUSPID AND LEFT-SIDED VALVE SURGERY IN A RHEUMATIC POPULATION

by

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DECLARATION

I MANDHIR MUNASUR, declare that:

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THE OUTCOME OF PATIENTS UNDERGOING SIMULTANEOUS TRICUSPID AND LEFT-SIDED VALVE SURGERY IN A RHEUMATIC POPULATION

ABSTRACT

Background

In the context of endemic left-sided rheumatic heart disease, tricuspid valve disease requiring surgical intervention merits closer scrutiny in order to analyse surgical outcomes with presently employed techniques.

Aims

To evaluate the results of simultaneous tricuspid valve surgery for severe functional tricuspid regurgitation in rheumatic heart disease at the time of left-sided valve surgery.

Materials and methods

A retrospective analysis of the perioperative and follow-up data of 30 patients who underwent tricuspid valve surgery with concomitant mitral and/or aortic valve replacement between July 2003 and December 2011 was undertaken.

Patients referred for left-sided valve replacement surgery with clinically and echocardiographically documented severe functional tricuspid regurgitation in the presence of tricuspid annular dilatation, were submitted for combined valvular procedures.

Outcomes were analysed by evaluation of the perioperative and 2-year follow-up clinical and echocardiographic data.

Results

There was a statistically significant improvement in the following parameters at 6 weeks postoperatively: New York Heart Association functional class, tricuspid annular diameter (p 0.001), pulmonary artery systolic pressure (p 0.001), severity of tricuspid regurgitation ($p<0.001$) and tricuspid transvalvular gradient (p 0.004).

Preoperative (p 0.013) and postoperative pulmonary hypertension ($p<0.002$) were demonstrated to be associated with the development of major adverse cardiovascular events. There were no identifiable predictors for the development of severe residual postoperative tricuspid regurgitation. The development of severe residual postoperative tricuspid regurgitation was not associated with the occurrence of major adverse cardiovascular events. The technique of tricuspid valve repair did not impact on the occurrence of major adverse cardiovascular events or on the development of severe residual postoperative tricuspid regurgitation. A satisfactory outcome was observed in 40% of the study population.

Conclusion

The immediate results of tricuspid valve surgery for severe functional tricuspid regurgitation in rheumatic heart disease favour surgical intervention. However, the persistence of severe tricuspid regurgitation adversely influenced long-term outcomes. Therefore, the management of rheumatic patients with functional tricuspid regurgitation should

encompass surgical strategies which result in a lower incidence of severe residual postoperative tricuspid regurgitation.

CHAPTER 1

INTRODUCTION

TRICUSPID VALVE ANATOMY AND PHYSIOLOGY

The tricuspid valve is trileaflet in structure and is the most apically placed heart valve with the largest orifice amongst the four valves[1,2]. The valve orifice is on average between 6-10cm^2 in adults. Anatomically, the valve apparatus comprises leaflets, annulus, chordae tendinae and papillary muscles.

The leaflets are designated anterior, posterior and septal and have indentations in their free edges between the leaflets which are referred to as commissures: anteroseptal, anteroposterior and posteroseptal. The anterior leaflet is the largest, is usually semicircular in configuration and attaches to the anterior and septal walls of the right ventricle. The septal leaflet lies between the posteroseptal and anteroseptal commissures and attaches to the septal and posterior walls of the right ventricle. It is immediately related to the membranous ventricular septum. The posterior leaflet is the smallest, lies between the anteroposterior and posteroseptal commissures and attaches to the posterior wall of the right ventricle. Refer to figure 1.

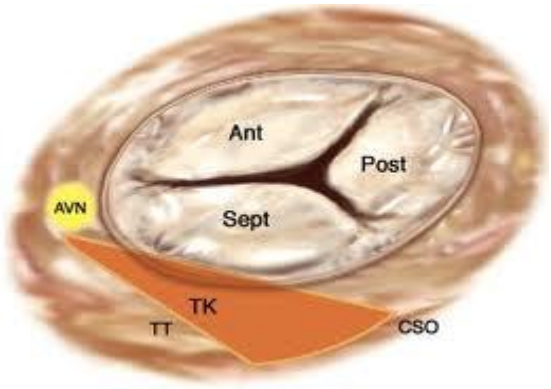

Figure 1. Surgical anatomy of the tricuspid valve. The triangle of Koch (TK) is indicated by the shaded area. Ant = anterior leaflet; AVN = atrioventricular node; CSO = coronary sinus orifice; Post = posterior leaflet; Sept = septal leaflet; TT = tendon of Todaro. From: Maurizio Taramasso, MD, Hugo Vanermen, MD, Francesco Maisano, MD, Andrea Guidotti, Giovanni La Canna, MD, Ottavio Alfieri, MD. The Growing Clinical Importance of Secondary Tricuspid Regurgitation.J Am CollCardiol 2012; 59(8):703-710.

The tricuspid annulus is oval-shaped and is located at the right atrio-ventricular junction. The right fibrous trigone provides attachment to the annulus only where the septal leaflet and anteroseptal commissure insert. The remaining annulus is unattached and the connective tissue of the anterior and posterior leaflets fuse with the subendocardial tissue where the leaflets attach directly to the myocardium[3]. This relatively unsupported area of the tricuspid annulus represents the site of potential annular dilatation in response to right ventricular dilatation. The normal tricuspid valve annular diameter in adults is 28±5mm[4].

An average of 25 chordae tendinae insert into the tricuspid valve leaflets, providing attachment to the papillary muscles; 7 attach to the anterior leaflet, 6 to the posterior leaflet, 9 to the septal leaflet and 3 to the commissures[3]. The chordae are described according to their respective configuration as being either fan-shaped, rough zone, basal, free-edge or deep[3].

The tricuspid valve has 3 groups of integral papillary muscles, each set comprising up to 3 muscles[2]. Chordal insertion from each set of papillary muscles is into 2 adjacent leaflets. The anterior papillary muscle attaches to the anterior wall of the right ventricle and provides chordal attachment to the anterior and posterior leaflets. The posterior papillary muscle attaches to the posterior wall of the right ventricle and provides chordal attachment to the posterior and septal leaflets. In contrast, septal leaflet chordae tendinae arise directly from the interventricular septum.

The tricuspid leaflets open in diastole with expansion of the valve orifice to facilitate atrio-ventricular blood flow. Systolic contraction of the orifice is intended to result in effective valve closure; however, a degree of regurgitation demonstrated in healthy subjects using colour-flow Doppler echocardiography is normal[2].

The tricuspid valve functions within a low-pressure, high-volume system[1]. Peak early tricuspid valve inflow velocity is less than 1m/s and the mean gradient across the tricuspid orifice during diastole is less than 2mm Hg[2]. Right ventricular systolic pressure is 20-25mm Hg; end-diastolic pressure is equivalent to right atrial peak pressure of 3-4mm Hg[1]. Pulmonary artery systolic pressure of 20-25mm Hg is equivalent to right ventricular systolic pressure[1]; right ventricular diastolic pressure is about 10mm Hg[1].

TRICUSPID VALVE PATHOLOGY

Disease of the tricuspid valve is classified as being either primary or secondary. Primary disease refers to intrinsic or organic disease of the valve itself, whilst secondary disease is due to impaired leaflet coaptation on the basis of right ventricular or tricuspid annular

dilatation. This is commonly referred to as “secondary” or “functional” tricuspid regurgitation and is a direct consequence of left-sided valvular disease.

Primary disease may be a result of congenital cardiac malformations, rheumatic heart disease, infective endocarditis, carcinoid heart disease, cardiac tumours, trauma, degenerative valve disease, iatrogenic or toxic valvulopathy[2].

Secondary, or functional tricuspid regurgitation occurs in the presence of right ventricular hypertension, dilatation or failure, most commonly in response to advanced left-sided rheumatic heart valve disease[2]. Functional tricuspid regurgitation is accompanied by annular dilatation and leaflet tethering (apical displacement of the tricuspid leaflets). To a lesser, extent, functional tricuspid regurgitation occurs as a result of segmental or global right ventricular dysfunction; the former on an ischaemic basis and the latter due to cardiomyopathy.

PATHOGENESIS OF FUNCTIONAL TRICUSPID REGURGITATION IN LEFT-SIDED VALVULAR DISEASE

In the presence of left-sided rheumatic valvular disease, the underlying condition leads to the development of mitral regurgitation[5]. Rheumatic heart disease may also cause mitral stenosis. Both forms of mitral valve disease cause increased left atrial pressure, resulting in pulmonary hypertension, right ventricular dysfunction, enlargement, and eventually tricuspid regurgitation[5]. A consequence of increased left atrial pressure is left atrial dilatation; a phenomenon directly related to atrial fibrillation and tricuspid annular dilatation[5]. Tricuspid annular dilatation is considered to be the “substratum” for the

development of tricuspid regurgitation[5]. Rheumatic heart disease may also result in organic disease of the tricuspid valve, and directly result in tricuspid regurgitation.

Various mechanisms are proposed in the development of functional tricuspid regurgitation. Tricuspid annular dilatation and tricuspid leaflet tethering in tandem disrupt the balance among tricuspid leaflet size, annular orifice area and spatial orientation of the valve apparatus, resulting in impaired leaflet coaptation and the development of tricuspid regurgitation[6]. The tricuspid annulus undergoes changes in three-dimensional geometry; it occupies a greater area, becomes flatter and circular in shape and the annular excursion is diminished during the cardiac cycle[7]. In summary, the normal geometric relationships of the tricuspid leaflets, chordae and papillary muscles are distorted by functional tricuspid regurgitation and right ventricular dilatation, resulting in tricuspid leaflet tethering and restricted coaptation[7].

PATHOPHYSIOLOGY OF FUNCTIONAL TRICUSPID REGURGITATION

Tricuspid regurgitation is regarded as a progressive condition. The right atrium and ventricle dilate due to volume overload. Eventually, right ventricular systolic dysfunction supervenes; increased diastolic pressure is accompanied by displacement of the interventricular septum towards the left ventricle during diastole[8]. This phenomenon has been termed "restriction-dilatation syndrome[8]," and is characterised by elevated pressure and expanding volume of one chamber compressing an adjacent chamber resulting in elevated pressure in the latter.

ASSESSMENT OF THE SEVERITY OF TRICUSPID REGURGITATION

Tricuspid valve analysis is mandatory in the presence of tricuspid regurgitation[4]. The imaging modality of choice is three-dimensional transthoracic echocardiography. Trans-oesophageal echocardiography is recommended in the presence of suboptimal transthoracic echocardiographic images[4].

Various combinations of qualitative, semi-quantitative and quantitative echocardiographic parameters have been recognised to confer varying degrees of severity to tricuspid regurgitation which may be described as mild, moderate or severe[4]. The qualitative parameters are: tricuspid valve morphology, the size of the colour-flow regurgitant jet and the density of the continuous wave jet signal. The semi-quantitative parameters are: width of the vena contracta, proximal isovelocity surface area radius, hepatic vein flow and tricuspid inflow characteristics. The quantitative parameters are: effective regurgitant orifice area dimension and combined regurgitant volume and right atrial/right ventricular/inferior vena caval dimension.

IMPACT OF TRICUSPID REGURGITATION ON SURVIVAL

Moderate or greater tricuspid regurgitation has been demonstrated to confer decreased survival in men regardless of left ventricular ejection fraction or pulmonary artery pressure[9]. Severe tricuspid regurgitation has been associated with a poor prognosis, independent of age, biventricular systolic function, right ventricular size or inferior vena caval dilatation[9]. Mild-or-less tricuspid regurgitation is not associated with adverse outcome[9]. The exact reason for increased mortality with significant tricuspid regurgitation remains undetermined.

PROGNOSTIC IMPLICATIONS OF FUNCTIONAL TRICUSPID REGURGITATION IN PATIENTS WITH MITRAL VALVE DISEASE

The presence of tricuspid regurgitation following mitral valve replacement predicts poor outcome[10].

Moderate-to-severe tricuspid regurgitation during follow-up has been found to be an independent predictor of New York Heart Association functional class 3 or 4 heart failure, heart failure-related death, and all-cause mortality during follow-up[11]. A 5-year survival rate of 50% in rheumatic heart disease patients with the clinical and echocardiographic features of severe tricuspid regurgitation following mitral valve surgery has been documented[12]. Significant tricuspid regurgitation necessitating tricuspid valve surgery has been shown to predict poor survival in patients undergoing left-sided valve surgery[13]. Functional tricuspid regurgitation occurring late after mitral valve surgery has been demonstrated to be related to diminished overall long-term survival and a worse long-term functional status; in addition, re-operation for late severe functional tricuspid regurgitation has been associated with a uniformly poor prognosis and high early and late mortality[14].

There is also evidence that untreated tricuspid regurgitation following mitral valve replacement is associated with a diminished cardiac output response to exercise which deteriorates in the face of progressive tricuspid valve dysfunction, eventually requiring reoperation[8].

BASIS FOR INTERVENTION IN FUNCTIONAL TRICUSPID REGURGITATION

Functional tricuspid regurgitation was previously regarded as a benign condition that resolved spontaneously after correction of left-sided valvular heart disease. Left untreated, it is now known not to resolve after mitral valve surgery in a high proportion of patients, causing persistence of moderate or severe tricuspid regurgitation at mid-term follow-up and impacting adversely on survival[15].

Reoperation on the tricuspid valve for persistent tricuspid regurgitation after mitral valve surgery is associated with a high surgical risk; the presence of irreversible right ventricular dysfunction prior to reoperation may be the reason for poor long-term results[8]. Correction of tricuspid annular dilatation by adoption of a stage-specific therapeutic strategy as the cornerstone of intervention in functional tricuspid regurgitation is believed to offer improved short-and long-term outcomes[15]. The emergence of a need to pre-emptively identify patients at risk of progression of tricuspid regurgitation has been in response to poor outcomes of patients undergoing reoperative surgery for late severe tricuspid regurgitation[16].

MANAGEMENT OF FUNCTIONAL TRICUSPID REGURGITATION IS CONTENTIOUS

In an early report, it has been suggested that tricuspid regurgitation regresses after mitral valve replacement and that concomitant tricuspid surgery is not required[10]. This view is no longer held with the emergence of new evidence[14].

In contemporary surgical practice, however, despite the existence of a general agreement for simultaneous interventional tricuspid valve surgery in cases of severe regurgitation in

the setting of left-sided valve surgery, the current guidelines offer unclear indications for patients with mild-to-moderate tricuspid regurgitation[17].

Tricuspid valve repair based on tricuspid annular dilatation has been shown to improve functional status irrespective of the degree of regurgitation[18]. This is counterbalanced by a high rate of recurrence of tricuspid regurgitation after interventional surgery, independent of the surgical technique[19]. In addition, there is disagreement over the best surgical technique for tricuspid valve repair[5].

A review of the guideline indications for concurrent tricuspid valve repair demonstrates that severe tricuspid regurgitation at the time of mitral valve surgery is the only definite indication for intervention (Class 1)[20]. There is no apparent consensus on the management of mild functional tricuspid regurgitation; similarly, the management of moderate-to-severe tricuspid regurgitation is open to interpretation[19,20]. There have even been proponents for "prophylactic" annuloplasty in order to avoid disease progression[18].

The enduring questions that guide surgical decision-making in functional tricuspid regurgitation may be summarised thus[8]: When should one repair or replace the tricuspid valve in association with surgery for left-sided valve disease? What should be done with mild-to-moderate tricuspid regurgitation? How does one predict those patients who will return after mitral valve surgery with clinically significant tricuspid regurgitation?

PRINCIPLES OF SURGICAL MANAGEMENT OF FUNCTIONAL TRICUSPID REGURGITATION

The principal determinants of tricuspid regurgitation must be addressed for surgical treatment of functional tricuspid regurgitation to be effective: increased right ventricular afterload, annular dilatation and right ventricular dysfunction[20].

Correction of the left-sided valvular lesion and left ventricular dysfunction will result in reduced pulmonary hypertension and reduced right ventricular afterload. Correction of the left-sided valvular lesion, elimination of tricuspid regurgitation and reduction of pulmonary hypertension will improve right ventricular dysfunction.

The foundation of current surgical therapy for severe functional tricuspid regurgitation is tricuspid valve repair which addresses annular dilatation and restores annular geometry, facilitating leaflet coaptation[20]. The surgical armamentarium for functional tricuspid regurgitation is divided between tricuspid repair techniques and tricuspid valve replacement. Tricuspid valve repair procedures address functional tricuspid regurgitation at 3 anatomical levels: annulus, commissure and leaflet[21] and although many techniques have been described, most are derivatives of 2 fundamental approaches: suture annuloplasty and ring annuloplasty[20]. Tricuspid valve repair is considered preferable to replacement whenever technically possible. Tricuspid valve replacement is usually reserved for tricuspid valve disease of organic origin.

CHAPTER 2

OVERVIEW AND LITERATURE REVIEW

INCIDENCE OF FUNCTIONAL TRICUSPID REGURGITATION IN MITRAL VALVE DISEASE

Functional tricuspid regurgitation is reported to occur relatively frequently in the presence of mitral valve disease in the surgical literature.

More than a third of patients with mitral stenosis have at least moderate tricuspid regurgitation[10]. In patients with rheumatic heart disease, clinically severe tricuspid regurgitation has been documented in 23% to 37% of patients after mitral valve replacement[10].

In rheumatic patients, echocardiographically moderate or severe late tricuspid regurgitation has been reported in up to 68% of patients and is characteristically diagnosed late after mitral valve replacement, 10 years on average[10].

PROGNOSIS OF FUNCTIONAL TRICUSPID REGURGITATION IN MITRAL VALVE DISEASE

Only as recently as 2008, has the prognostic role of untreated functional tricuspid regurgitation been delineated[22]. The authors concluded that moderate-or-more functional tricuspid regurgitation, left untreated at the time of surgical intervention for mitral regurgitation, would impair 5-year survival, as well as survival in New York Heart Association functional class 1-2, based on the premise that functional tricuspid regurgitation is likely to progress.

In three retrospective studies[18,23,24], it has been shown that leaving functional tricuspid regurgitation untreated at the time of mitral valve surgery results in more tricuspid regurgitation at follow-up despite correction of co-existent left-sided disease.

PREDICTORS OF RESIDUAL TRICUSPID REGURGITATION AFTER MITRAL VALVE SURGERY

The uncertainty whether preoperative functional tricuspid regurgitation will regress or progress after surgery challenges surgical decision-making during intervention for left-sided valve disease.

In a series of 174 patients undergoing mitral valve surgery without tricuspid valve intervention, severe tricuspid regurgitation was documented in 16% of patients late after mitral valve replacement[24]. The risk factors identified for residual tricuspid regurgitation were: a left atrial diameter >60mm and the presence of atrial fibrillation. Mechanisms postulated to be responsible for the high prevalence of late tricuspid regurgitation were: persistent pulmonary hypertension, right ventricular dysfunction, tricuspid annular dilatation, a postoperative increase in cardiac output resulting in diminished regression of tricuspid annular dilatation and the presence of more-than-mild tricuspid regurgitation.

In a study of 70 patients with functional ischaemic mitral regurgitation who underwent coronary revascularization and mitral valve repair, preoperative functional tricuspid regurgitation was present in 30% of cases[25]. In 57% of the cases, the tricuspid regurgitation was ignored and post surgery the incidence of tricuspid regurgitation increased to 50% irrespective of whether it was repaired or ignored. The presence of tricuspid regurgitation

increased during follow-up, peaking at 70% at 3 years. Preoperative annular dilatation was established to be a predictor of late tricuspid regurgitation.

Multiple clinical variables were shown to be independent risk factors for the development of late severe tricuspid regurgitation in 638 patients who had mild tricuspid regurgitation and who underwent successful left-sided valve surgery without any tricuspid procedure[26]. The baseline risk factors were reported to be: age, female gender, rheumatic aetiology and atrial fibrillation.

The influence of subvalvar preservation techniques on the development of late severe tricuspid regurgitation after mitral valve replacement was investigated in 801 patients who did not undergo any tricuspid procedure[27]. It was concluded that although early surgical intervention for tricuspid regurgitation may be recommended in selected patients, complete preservation of the mitral subvalvar apparatus and routine surgical elimination of atrial fibrillation could significantly reduce its incidence.

The impact of tricuspid leaflet tethering in functional tricuspid regurgitation on recurrent or residual tricuspid regurgitation following tricuspid annuloplasty was studied in 39 patients[28]. Of these, 33 patients had concomitant mitral valve procedures. Preoperative tricuspid leaflet tethering height and area were found to be risk factors for tricuspid repair failure, prompting the need for additional surgical strategies to overcome this phenomenon.

GUIDELINES FOR THE MANAGEMENT OF FUNCTIONAL TRICUSPID REGURGITATION

Guidelines from both the American College of Cardiology/American Heart Association and the European Society of Cardiology, assign a class 1 recommendation for tricuspid valve

repair in patients with severe tricuspid regurgitation undergoing left-sided valve surgery[10,29]. The European guidelines assign a class 2a recommendation for concomitant tricuspid valve repair in patients with a tricuspid annular diameter >40mm or moderate tricuspid regurgitation[29]. The American guidelines assign a class 2b recommendation for patients with less-than-severe tricuspid regurgitation[10]. A class 2a recommendation is also assigned by the European guidelines for tricuspid valve repair in patients with symptomatic, isolated tricuspid regurgitation late after mitral and/or aortic valve surgery, on condition that left-sided myocardial or right ventricular dysfunction and severe pulmonary hypertension are absent[29].

SURGICAL MANAGEMENT OF FUNCTIONAL TRICUSPID REGURGITATION

The current surgical repertoire for functional tricuspid regurgitation is divided between tricuspid valve repair techniques and tricuspid valve replacement. Controversy exists over the best surgical technique for tricuspid valve repair[5] whilst prosthetic replacement of the tricuspid valve is accompanied by valve-related complications. It is always desirable to preserve the native tricuspid valve as far as possible, if technically feasible; hence repair techniques are favoured above valve replacement.

The recurring questions in the literature with respect to decision-making in tricuspid valve surgery are[8]: What is the choice between tricuspid valve repair and replacement? What is the efficacy of different methods of repair? What type of prosthesis is to be selected if the valve is replaced?

Traditionally, the basic principles of tricuspid valve repair involve the following techniques[31]:

1. Techniques that obliterate some of the anterior and posterior leaflet tissue whilst simultaneously reducing the corresponding annular dimension, constructing one or more pleats along its length.

2. Techniques that fix the anterior and posterior leaflet annulus to a partial prosthetic ring, which may be rigid or pliable in design and reduce the annular dimension by application of wide suture-spacing at the annulus and narrow suture-spacing at the ring.

3. Techniques that incorporate a sliding plasty of the leaflets with annular reduction, performed using a prosthetic ring or by the construction of pleats.

4. Techniques that shorten the annulus by means of an incomplete purse-string suture embedded in the atrioventricular junction adjacent to the anterior and posterior leaflets, extending from the anteroseptal to the posteroseptal commissures.

Tricuspid valve repair procedures address functional tricuspid regurgitation at 3 anatomical levels: annulus, commissure and leaflet[21].

Annular Procedures

Techniques that address tricuspid annular dilatation comprise suture annuloplasty and ring annuloplasty. Refer to figure 2.

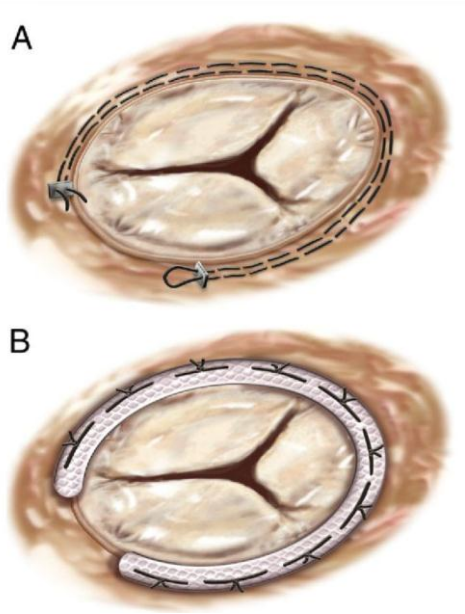

Figure 2. Tricuspid annular procedures. (A) Suture annuloplasty repair: a single suture is placed around the tricuspid annulus, avoiding the area of the atrioventricular node. The suture is tied, completing the annuloplasty. (B) Ring annuloplasty repair: a sizer measuring the intertrigonal distance is used to determine the ring size. Multiple interrupted sutures are placed at the atrioannular junction. From: Maurizio Taramasso, MD, Hugo Vanermen, MD, Francesco Maisano, MD, Andrea Guidotti, Giovanni La Canna, MD, Ottavio Alfieri, MD. The Growing Clinical Importance of Secondary Tricuspid Regurgitation.J Am CollCardiol 2012; 59(8):703-710.

Suture Annuloplasty

Suture annuloplasty techniques aimed at annular reduction are the De Vega annuloplasty and its modification. The original De Vega annuloplasty plicated both the anterior and posterior annulus using a continuous, double-layer pledgeted non-absorbable suture placed in the atrio-ventricular junction adjacent to the annulus from the anteroseptal to posteroseptal commissures. The sutures are then tightened to produce a purse-string effect, reducing the length of the anterior and posterior annuli and resulting in adequate

leaflet coaptation. The desired annular reduction is best achieved using a tricuspid annuloplasty obturator conforming to the dimension of the septal leaflet of the tricuspid valve.

The problem of suture dehiscence from the annulus was overcome by Antunes and Girdwood in a modification described in 1983 in which each suture was buttressed with a synthetic pledget[8]. Although these techniques are quick, inexpensive and technically simple, they are less reproducible and their results are less predictable than those of ring annuloplasty.

Uncertainty over the extent to which the dilated tricuspid annulus should be reduced using suture annuloplasty techniques has led to annular stenosis and residual tricuspid regurgitation postoperatively. The development of techniques to selectively reduce the dilated anterior and posterior tricuspid leaflet annuli without reducing the active surface of the valve leaflets has been described by Yiwu and others[33]. Their procedure is based on an exact quantitative repair technique using purpose-made tricuspid obturators to individualise the change in annular dimension to the physiological and anatomical characteristics of each patient's tricuspid annulus and offers an alternative technique to ensure efficacy of tricuspid repair when an annuloplasty ring is not used.

Ring Annuloplasty

Tricuspid ring annuloplasty was described in 1971 by Carpentier where a reduction annuloplasty of the anterior and posterior tricuspid annulus was accomplished using a pre-shaped rigid prosthetic ring[32].

In contemporary practice, tricuspid annuloplasty rings or bands may be partial or complete and flexible, semi-rigid or rigid in design and construction[20]. The dimension of the base of the septal leaflet of the tricuspid valve dictates the size of the ring or band employed. An additional method to determine the size of prosthesis to be used is by comparing the tricuspid obturator to the combined surface area of the anterior and posterior tricuspid leaflets[20].

Non-absorbable, pledgeted mattress sutures are placed circumferentially at the junction of the annulus and right ventricular free-wall, with wider suture placement on the annulus and narrower corresponding suture placement on the prosthetic sewing ring to produce annular plication predominantly along the length of the posterior leaflet. The re-orientated geometry allows occlusion of the valve orifice primarily by anterior and septal leaflet tissue. Rigid and semi-rigid rings are believed to restore the three-dimensional geometry of the tricuspid annulus in a fixed systolic position (remodelling annuloplasty)[20].

The use of a partial ring or band prosthesis avoids inadvertent suture placement into the conduction tissue related to the septal leaflet, thereby minimizing the occurrence of postoperative conduction block. These devices also stabilize the anterior and posterior annulus, the anatomical areas known to be most prone to dilatation. The use of a complete ring confers complete protection against future annular dilatation, but carries an increased risk of iatrogenic conduction block. This potential risk is minimised by placement of sutures through the base of the septal leaflet instead of through the annulus in the region of the conduction tissue. It appears that the main benefit from employing a rigid ring over a

flexible band is that the dimension of the septal annulus is both normalised and effectively stabilised, reducing the incidence of late regurgitation.

Commissural Procedures

Suture bicuspidization commissuroplasty, a technique described by Kay and others in 1965 transforms the tricuspid valve into a bicuspid valve structure[34]. This is accomplished by plicating the annulus along the posterior leaflet using 2 concentric, pledgeted non-absorbable sutures. The sutures are tied to obliterate the posterior leaflet, producing a bicuspid right atrioventricular valve. Refer to figure 3. The disadvantage of this technique is that it results in posterior leaflet atrophy and does not address the tendency of the anterior annulus to dilate[20]. There is additional technical difficulty in deciding how much of the posterior leaflet to plicate.

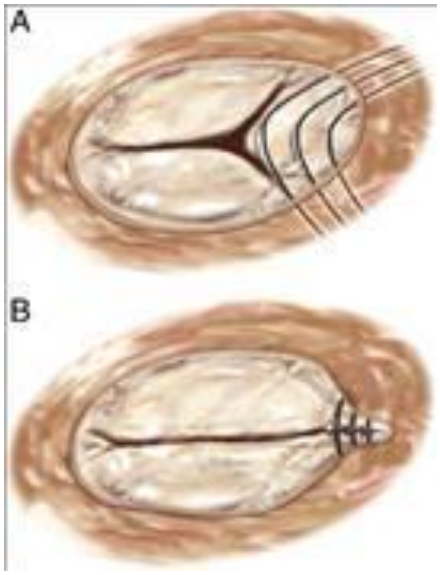

Figure 3. Suture bicuspidization commissuroplasty. (A) Tricuspid valve bicuspidization is accomplished by plicating the annulus along the posterior leaflet. (B) The sutures are tied, obliterating the posterior leaflet, creating a bicuspid valve. From: Maurizio Taramasso, MD, Hugo Vanermen, MD, Francesco Maisano, MD, Andrea Guidotti, Giovanni La Canna, MD, Ottavio Alfieri, MD. The Growing Clinical Importance of Secondary Tricuspid Regurgitation.J Am CollCardiol 2012; 59(8):703-710.

Leaflet Procedures

The phenomenon of leaflet tethering has been described as a risk factor for failure of valve repair in functional tricuspid regurgitation[28]. Severe tethering is defined echocardiographically as a tethering height (the distance between the tricuspid annular plane and the coaptation point between the anterior and septal leaflets) greater than 8mm at mid-systole in a four-chamber view[35]. When severe tethering is present, additional techniques have been described in conjunction with ring annuloplasty in order to add durability to the repair[20].

Dreyfuss and others pioneered a technique for treating severe tricuspid regurgitation due to severe tricuspid leaflet tethering by augmenting the anterior tricuspid leaflet with a patch of autologous pericardium[35]. This manoeuvre increases the size of the anterior leaflet, hence its surface area of coaptation, thus permitting increased leaflet coaptation to occur in the presence of decreased right ventricular tension. The repair is reinforced using a rigid annuloplasty ring. The major advantage of this procedure is that leaflet coaptation is allowed to occur within the right ventricle at the level of the tethered septal and posterior leaflets, whilst simultaneously preserving leaflet mobility.

The surgical management of complex tricuspid valve pathology has encompassed challenging reconstructive procedures and has been associated with suboptimal outcomes. A surgical technique whereby the central portion of the free edges of the tricuspid leaflets are sutured together to produce a “clover” shaped valve has been proposed by De Bonis and others to improve the efficacy of valve repair in the context of complex lesions, not manageable exclusively by annuloplasty[36]. Refer to figure 4. This represents a functional,

rather than an anatomical repair and has been postulated to be effective in any type of tricuspid insufficiency on the basis of complex mechanisms such as leaflet prolapse, flail or retraction[37]. Significantly, tricuspid valve competence was reported to be restored even in the presence of severe right ventricular dilatation and pulmonary hypertension.

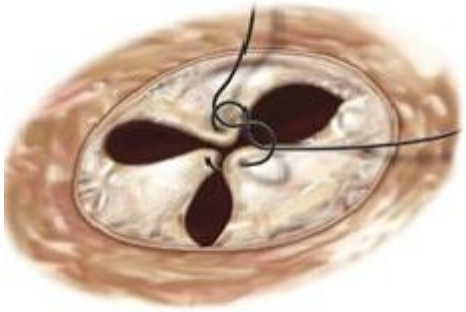

Figure 4. The Clover technique. The middle parts of the free edges of the tricuspid leaflets are sutured together, producing a clover-shaped valve. From: Maurizio Taramasso, MD, Hugo Vanermen, MD, Francesco Maisano, MD, Andrea Guidotti, Giovanni La Canna, MD, Ottavio Alfieri, MD. The Growing Clinical Importance of Secondary Tricuspid Regurgitation.J Am CollCardiol 2012; 59(8):703-710.

Tricuspid valve replacement

Although preservation of the native valve whenever technically feasible is one of the tenets of contemporary cardiac surgery, replacement of the tricuspid valve is sometimes necessary. The available options for tricuspid valve replacement are either a mechanical or biological prosthesis or a mitral homograft. The major operative complication is that of heart block arising from suture injury to the conducting tissue, hence preservation of the tricuspid leaflets and subvalvar apparatus is desirable in order to minimize the risk of injury. Everting, pledgeted mattress sutures are used for implantation of a mechanical valve and similar suture material is used in a supra-or-intra-annular configuration for implantation of a bioprosthesis. It is also recommended that the procedure be performed with the heart beating, employing continuous electrocardiographic monitoring in order to detect rhythm

disturbance arising from aberrant suture placement. The placement of temporary epicardial pacing electrodes is mandatory for the pre-emptive management of potential dysrhythmias.

Partial replacement of the tricuspid valve using mitral homograft tissue has been reported in the setting of right-sided infective endocarditis when repair techniques are not feasible, and represents an alternative to prosthetic replacement of the tricuspid valve[38]. In this series, the tricuspid valve was reinforced using a rigid prosthetic ring. The choice of mitral, rather than tricuspid valve tissue for implantation is influenced by the fact that mitral tissue is of superior quality and has more favourable handling characteristics than tricuspid tissue.

Percutaneous options

Experimental reports describing percutaneous approaches to tricuspid valve disease in animals have emerged as early as 2005 when a percutaneous tricuspid valve constructed from a bovine jugular venous valve mounted to a self-expanding nitinol frame was deployed in sheep via the jugular vein[30]. The anatomical structural relationships of the right atrium present unique challenges to this approach with respect to device placement and an additional consideration is that of thrombogenicity induced by the low pressure and flow characteristics of the right heart.

TRICUSPID VALVE REPAIR: LONG-TERM RESULTS

The various techniques of tricuspid valve repair described in the literature encompass suture and ring annuloplasty, bicuspidization, anterior leaflet augmentation and the clover-leaf repair. In the analysis of the long-term results of the various applicable techniques, it is mandatory to consider factors such as functional class, presence of congestive heart failure, recurrence of moderate-to-severe tricuspid regurgitation, event-free survival (freedom from thromboembolism, major bleeding event, infective endocarditis, tricuspid valve reoperation and death) and actuarial survival.

In a thirty year retrospective assessment of outcome after tricuspid valve surgery, Guenther and colleagues discuss their findings from a series of 310 patients who underwent tricuspid valve repair out of a cohort of 416 consecutive patients submitted to tricuspid valve surgery with or without concomitant cardiac surgical procedures[39]. They emphasise that patients who require tricuspid valve surgery constitute a high-risk group reflected by an advanced stage of heart disease often accompanied by severe right ventricular dysfunction. Ten-year actuarial survival after tricuspid valve repair was 47% and freedom from tricuspid valve reoperation at the same interval was 83%.

Carrier and co-workers reported the results of 3 surgical techniques employed in the repair of functional tricuspid insufficiency in 463 patients over 25 years[40]. They noted a mean 5-, 10- and 15-year patient survival of 82%, 58% and 30% respectively in the group undergoing suture annuloplasty; 76%, 54% and 36% survival for the corresponding period in the group undergoing flexible band implantation and 88% survival at 5 years for the prosthetic ring annuloplasty group. The mean freedom rate from tricuspid repair failure was 95%, 93% and

72% at 5, 10 and 15 years respectively for the suture annuloplasty group and 97%, 87% and 66% at 5, 10 and 15 years for the flexible band group respectively. At 5 years the mean freedom rate from repair failure for the prosthetic ring annuloplasty cohort was 94%. They concluded that all 3 techniques of tricuspid valve repair resulted in a low failure rate and in good patient survival at long-term follow-up.

Publishing their experience with the long-term results of triple valve surgery, Carrier and others described their findings in 66 patients undergoing tricuspid valve repair using a suture annuloplasty, flexible ring or prosthetic ring technique during simultaneous mitral and aortic valve replacement with either mechanical or biological prostheses, including reoperations[41]. Patient survival at 1, 5 and 10 years averaged 80%, 75% and 41% respectively for patients undergoing primary surgery and 70%, 57% and 50% respectively for patients undergoing reoperative surgery. They concluded that triple valve surgery results in acceptable long-term survival with both mechanical and biological prostheses.

The long-term clinical outcome was investigated by Onoda and co-investigators in 45 patients with functional tricuspid regurgitation managed by rigid ring annuloplasty[42]. The mean follow-up was 96.7 months. Actuarial survival at 10 years was 68.3% with satisfactory regression of tricuspid regurgitation and functional class. The actuarial rate of freedom from tricuspid valve reoperation at 10 years was 97.5%. Their conclusion was that rigid ring annuloplasty was acceptable for repair of functional tricuspid regurgitation as well as long-term improvement in functional status.

In a study of 110 patients undergoing a De Vega annuloplasty for functional tricuspid regurgitation at the time of left-sided valvular surgery, Abe and others reported their results

after a mean follow-up of 22 months[43]. They demonstrated a significant improvement in haemodynamics and functional class postoperatively as well as a late mortality of 2.7%. In addition, their actuarial survival rate at 10 years was 85.8% and the actuarial rate of freedom from tricuspid valve reoperation was 96.7%.

Bernal and associates examined long-term outcomes after combined mitral and tricuspid valve repair in 153 consecutive patients with rheumatic valvular disease[44]. The mean follow-up duration was 15.8 years. They demonstrated poor long-term results with a late mortality of 60.1% and a high reoperation rate for both the mitral and tricuspid valve. They concluded that the use of a prosthetic tricuspid annuloplasty ring was associated with a reduced incidence of tricuspid valve reoperation.

TRICUSPID VALVE REPLACEMENT: DETERMINANTS OF EARLY AND LONG-TERM OUTCOMES

Poor outcomes have been historically documented following tricuspid valve replacement; high operative mortality rates, low rates of event-free survival and poor long-term survival. The preoperative factors associated with these results have been poorly understood and may serve to improve outcomes when selection for surgical intervention is modified accordingly.

The reported early mortality following tricuspid valve replacement ranges from 8.8-25% and 5-year actuarial survival ranges between 41-44%[45]. Valve-related events described in relation to event-free survival in the literature include thromboembolism (including stroke), valve thrombosis, structural valve dysfunction, major bleeding events, infective endocarditis, tricuspid valve reoperation and death.

In a study to determine the preoperative predictors of increased mortality and adverse outcome after tricuspid valve replacement, Topilsky and others identified advanced heart failure and echocardiographic evidence of increased right ventricular filling pressure to be the principal determinants of early outcome and survival in 189 patients undergoing tricuspid valve replacement[45].

In a series of 42 consecutive patients undergoing tricuspid valve replacement, Iscan and colleagues reviewed their experience in a cohort with a predominance of rheumatic valve disease and concluded that suboptimal short and long-term outcomes are influenced by aetiology, clinical presentation and pulmonary vascular haemodynamic parameters[46].

Carrier and others, in a series of 97 patients undergoing tricuspid valve replacement with 25-year follow-up data, concur that survival after tricuspid valve replacement is suboptimal, and is related to the clinical condition at the time of operation[47].

SUTURE VERSUS RING ANNULOPLASTY

The inevitable comparison between the techniques of suture and ring annuloplasty accompanies virtually every review of the literature on the subject of tricuspid valve repair.

From their series of 702 patients who underwent tricuspid valve repair utilizing either a De Vega or a ring annuloplasty, Tang and others sought to compare their long-term outcomes in patients with predominantly functional tricuspid regurgitation[48]. They illustrated significantly better long-term survival, event-free survival, freedom from recurrent tricuspid regurgitation and fewer tricuspid valve reoperations in the ring annuloplasty group. In

addition, they demonstrated by multivariate analysis that the use of an annuloplasty ring was an independent predictor of long-term survival.

The question of whether tricuspid ring annuloplasty is the superior technique of tricuspid valve repair was examined in a study by Guenther and colleagues[49]. Their study cohort included 717 patients undergoing tricuspid valve surgery, of whom 60% had a ring annuloplasty and 36% had a suture annuloplasty. The aetiology was functional tricuspid regurgitation in 67%. They concluded that the ring annuloplasty was associated with improved survival and a lower reoperation rate than suture annuloplasty.

A direct comparison of long-term outcomes among 194 patients who underwent tricuspid repair for functional regurgitation using either suture or ring annuloplasty was undertaken by Seitelberger and others[50]. Their results indicated that recurrence of tricuspid insufficiency and the need for tricuspid valve reoperation was greater in the suture annuloplasty group. Significantly, survival in the suture annuloplasty group was lower during follow-up.

Matsuyama and co-investigators compared the results of 45 patients managed by either suture or ring annuloplasty for functional tricuspid regurgitation[51]. They demonstrated a significant decrease in the recurrence of tricuspid regurgitation in those patients receiving a ring annuloplasty and conclude that the ring annuloplasty is the superior form of treatment for patients with functional tricuspid regurgitation.

The issue of whether tricuspid valve repair with an annuloplasty ring leads to an improved outcome over a conventional suture annuloplasty repair was addressed by Khorsandi and

co-workers in a review of 306 papers in the literature, of which 14 presented the best evidence to derive an answer[52]. They concluded that most studies supported the use of a ring annuloplasty over a suture annuloplasty.

VALVE CHOICE IN TRICUSPID VALVE REPLACEMENT

It is uniformly accepted that prosthetic valve replacement in the tricuspid position is challenged by similar complications documented in the mitral and aortic position. The incidence of thrombo-embolic and thrombotic complications with mechanical prostheses is of concern, whilst the problem of structural valve degeneration becomes relevant with bioprostheses. Although partial or total replacement of the tricuspid valve using homografts has been reported[38], their results remain inconclusive[8].

Kaplan and others debate the selection of the most suitable tricuspid prosthesis in their paper describing 129 tricuspid valve replacements over a 20 year period[53]. In a cohort where the mean age was 35.27 years, 97 patients received a mechanical prosthesis. They found that there was no statistically significant difference between the two recipient groups with respect to early mortality, re-replacement and mid-term mortality. However, their preference for a mechanical prosthesis was based on favourable haemodynamic characteristics and durability.

The early and late results of 60 patients who underwent tricuspid valve replacement were published by Scully and others after a mean follow-up of 75 months[54]. Bioprostheses were implanted in 47% of patients and 53% underwent mechanical valve replacement. The hospital morbidity and mortality were not significantly different between the recipient

groups. A late overall mortality of 32% was reported but no difference in survival or valve-related complications was documented between the mechanical and bioprosthetic groups. Their recommendation was for the implantation of a mechanical prosthesis in the tricuspid position in younger patients and also in patients receiving mechanical valves in the mitral or aortic position who require long-term anticoagulation therapy.

In a review of 146 consecutive patients who underwent tricuspid valve replacement over a 25 year period, Van Nooten and co-workers analysed early and late events after a mean follow-up of 92 months[55]. They reported 70 late deaths with an actuarial survival rate of 74% at 60 months and 25% at 14 years. Univariate analysis indicated that the incremental risk factors for late death were the type of tricuspid prosthesis used, the type of intraoperative myocardial preservation employed as well as the preoperative functional class. They conclude that considering the high operative risk and poor long-term survival associated with tricuspid valve replacement, a large-dimension bioprosthesis is preferred due to its good initial durability and low risk of valve-related events. However, a bileaflet mechanical valve is proposed in patients with better life expectancy.

DURABILITY AND RISK FACTORS FOR FAILURE

The fact that recurrent significant tricuspid regurgitation is reported consistently after repair of functional tricuspid regurgitation is a marker of the variable durability of current repair techniques reported in the literature.

An evaluation of the durability of different techniques of tricuspid valve repair was performed by Sales et al in order to analyse the risk factors for failure of repair[56]. They

demonstrated inferior durability of repair with suture annuloplasty and pericardial techniques.

McCarthy et al compared the durability of 4 different techniques of tricuspid annuloplasty in 790 patients undergoing surgery for functional tricuspid regurgitation[57]. Residual tricuspid regurgitation was reported in 14% of patients early after surgery for all types of annuloplasty. It was found that the severity of preoperative tricuspid regurgitation determined the risk of repair failure within the first 6 months. However, most indicators of poor durability appeared to be related to baseline patient characteristics; risk factors considered to be irreversible. Late risk of repair failure was associated not only with baseline patient characteristics such as left ventricular dysfunction, but also with avoidable factors such as the technique of annuloplasty and the presence of right ventricular pacing electrodes.

Kuwaki et al evaluated independent predictors for early and late unfavourable results in a group of 246 patients who underwent tricuspid valve repair for functional tricuspid regurgitation by means of either suture or ring annuloplasty[58]. The mean duration of follow-up was 7.8 years. The reoperation-free survival rate was 90% at 5 years and 84% at 10 years. The severity of preoperative tricuspid regurgitation was found to be a predictor of early residual tricuspid regurgitation and increasing severity of residual tricuspid regurgitation postoperatively was found to be a risk factor for late tricuspid valve reoperation.

In a 12-year follow-up of 156 patients with combined mitral and tricuspid valve disease who underwent mitral and tricuspid valve repair or replacement, Kay et al investigated the long-

term durability of tricuspid annuloplasty utilizing the bicuspidization technique[59]. They demonstrated an actuarial survival rate of 57% at 5 years and 44% at 12 years. Left ventricular ejection fraction was found to be the only significant determinant of survival after adjustment for age. The freedom rate from tricuspid valve reoperation at 10 years following tricuspid annuloplasty was shown to be 91%.

In their series of 236 patients undergoing tricuspid valve repair for mild-to-moderate functional tricuspid regurgitation in patients with rheumatic mitral valve disease, Kim and others published a freedom rate from moderate-to-severe tricuspid regurgitation at 5 years of 92.9% in patients undergoing tricuspid repair, versus 60.8% in a control group[60].

A study of 74 patients requiring tricuspid valve reoperation after a previous tricuspid repair using either suture or ring annuloplasty was described by Bernal et al after a mean follow-up of 14.2 years[61]. The mean interval between the primary repair and reoperation was 8.2 years. Reoperation was indicated because of progression of valve disease in 33.8% of patients and for early failure of tricuspid valve repair in 14.9% of patients.

RATIONALE FOR THE STUDY

Functional tricuspid regurgitation is a relatively common accompaniment in patients with mitral and to a lesser extent, aortic valve disease. Severe tricuspid regurgitation developing after successful left-sided heart valve surgery is difficult to manage and is associated with poor surgical outcomes and prognosis. Persistence of tricuspid regurgitation after operation for left-sided disease is associated with ongoing symptoms. This suggests that

early detection and appropriate intervention is needed when severe functional tricuspid regurgitation is found preoperatively.

Valvular heart disease of rheumatic aetiology forms a significant portion of the workload at the Cardiology and Cardiothoracic Units at Inkosi Albert Luthuli Central Hospital. Mild-to-moderate functional tricuspid regurgitation is observed commonly and is considered not to require surgical intervention at the time of left-sided valve replacement. The prevalence of severe functional tricuspid regurgitation in patients with clinically significant mitral valve disease is common, but is as yet undefined in this population, nor are the sequelae known in subjects in whom the tricuspid valve has been repaired.

This study is designed to study the outcome of patients with severe functional tricuspid regurgitation in a rheumatic population undergoing simultaneous tricuspid and left-sided valve surgery.

CHAPTER 3

AIMS, MATERIALS & METHODS

Aim

To evaluate the results of simultaneous tricuspid valve surgery for severe functional tricuspid regurgitation in rheumatic heart disease at the time of left-sided valve surgery.

Objectives

1. To define the relationship of pulmonary hypertension to long-term outcomes in patients with severe tricuspid regurgitation.

2. To assess the clinical impact of the development of late severe tricuspid regurgitation after successful left-sided valve surgery in terms of congestive heart failure requiring hospital admission, repeat tricuspid valve surgery and cardiovascular death (primary end-point).

3. To establish other factors associated with the development of major adverse cardiovascular events as well as the occurrence of late severe tricuspid regurgitation (secondary end-point) after successful left-sided valve surgery.

4. To assess the outcome of tricuspid valve surgery for functional tricuspid regurgitation in patients undergoing left-sided valve surgery in the context of rheumatic heart disease.

Hypothesis to be tested

Pulmonary hypertension is associated with persistence and exacerbation of tricuspid regurgitation even after successful left-sided valve surgery in rheumatic heart disease.

Summary of the proposed research

This study is designed to study the outcome of patients with severe functional tricuspid regurgitation undergoing simultaneous tricuspid valve surgery and left-sided valve repair/replacement for rheumatic valvular disease.

Materials and methods

A retrospective analysis of the perioperative and follow-up data of patients who underwent tricuspid valve surgery with concomitant mitral and/or aortic valve replacement between July 2003 and December 2011 at Inkosi Albert Luthuli Central Hospital, Durban, South Africa, was undertaken.

The study was given full ethics approval by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal on 16 October 2012.

The records of all patients who were submitted to tricuspid valve replacement or repair for severe functional tricuspid regurgitation together with replacement of rheumatic mitral and/or aortic valves were analysed, including those patients who had undergone previous tricuspid valve repair or replacement and/or previous aortic/mitral valve repair or replacement. Exclusion criteria were patients with congenital heart disease, those undergoing additional concomitant cardiac surgical procedures and left-sided valvular disease of non-rheumatic aetiology.

All patients were evaluated preoperatively by a combined Cardiology and Cardiothoracic Surgery service and submitted for surgery. The appraisal routinely consisted of a clinical evaluation, 12-lead electrocardiogram, chest radiograph, two-dimensional transthoracic echocardiogram and baseline haematological and biochemical investigations.

Patients referred for valve replacement surgery of left-sided lesions who had clinically and echocardiographically documented severe tricuspid regurgitation despite optimal medical therapy, in association with a dilated tricuspid annulus (end-diastolic diameter >32mm in adults), were submitted for combined valvular procedures (mitral and/or aortic valve replacement with simultaneous tricuspid valve repair or replacement). Surgery was performed after optimal pre-operative diuretic therapy to reduce congestive symptoms whenever the clinical condition of the patient permitted. Echocardiographic parameters recorded both pre- and postoperatively were: right atrial and ventricular diameter, left ventricular dimensions, tricuspid annular diameter, tricuspid valvular morphology, tricuspid leaflet mobility, tricuspid valve gradient, the presence of organic disease of the tricuspid valve and pulmonary artery systolic pressure.

Surgery was conventionally performed via median sternotomy with total cardiopulmonary bypass using ascending aortic and bicaval venous cannulation utilising moderate hypothermia and cold crystalloid cardioplegic arrest. Where applicable, left-sided procedures were completed first, followed by cardiac de-aeration and release of the aortic cross-clamp. Exposure of the tricuspid valve was either via a transverse or oblique right atriotomy facilitated by right atrial isolation and performed on the perfused, beating heart during rewarming. Routine intraoperative transoesophageal echocardiography was not

employed in this study. Surgical intervention for atrial fibrillation was not performed in this study population either. The technique of tricuspid repair and selection of replacement prostheses were at the discretion of the surgeon.

The preoperative demographics and clinical characteristics were extracted from inpatient records and comprised age, gender, primary valvular pathology, previous surgery, type of prosthesis implanted, type of tricuspid valve procedure and echocardiographic parameters (end-diastolic dimension, end-systolic dimension, ejection fraction, pulmonary artery systolic pressure, degree of tricuspid regurgitation, tricuspid annular dimension, tricuspid valve anatomy, tricuspid valve gradient, right ventricular dilatation and right atrial dilatation).

Two-dimensional transthoracic echocardiography and Doppler colour-flow estimation were performed using the Acuson Sequoia SC2000 ultrasound device (Siemens AG, Germany). Quantification of tricuspid regurgitation was facilitated by the apical four-chamber view and classified as mild, moderate or severe when the distal jet area was $<5cm^2$, 5-10cm^2 or $>10cm^2$ respectively.

In addition, the immediate echocardiographic outcome at 1 week was documented with respect to ejection fraction, pulmonary artery systolic pressure and degree of residual tricuspid regurgitation.

Standard anticoagulation regimens using coumadin-based therapy (warfarin) were used to achieve a target international normalised ratio (INR) of 2.0-4.0 where mechanical prostheses were implanted.

Outcomes were analysed by evaluating data from inpatient records and outpatient follow-up visits at 6 weeks, 6 months, 1 year and 2 years postoperatively comprising: NYHA functional class, diuretic therapy and echocardiographic parameters (end-diastolic dimension, end-systolic dimension, ejection fraction, pulmonary artery systolic pressure, degree of tricuspid regurgitation, tricuspid annular dimension, tricuspid valve gradient, right ventricular dilatation, right atrial dilatation and persistent tricuspid regurgitation/gradient across the tricuspid valve at last follow-up). In addition, telephonic follow-up was conducted after data capture in order to account for missing follow-up data. Data was not censored for death.

A significant tricuspid transvalvular gradient was defined as a gradient >2.0mm Hg. Prolonged ventilation was defined as mechanical ventilation for greater than 10 days. Prolonged intensive care unit stay was defined as an intensive care unit stay greater than 14 days. Prolonged hospital stay was defined as an inpatient stay greater than 30 days. Early mortality was defined as death during hospitalisation or within 30 days of surgery. The primary end-point was defined by the occurrence of any of the following major adverse cardiovascular events: death from a cardiovascular cause, the need for tricuspid valve reoperation or the presence of postoperative congestive cardiac failure requiring hospital admission. The secondary end-point was defined by the persistence of severe residual postoperative tricuspid regurgitation.

A satisfactory outcome was defined at 2-year follow-up by a combination of: postoperative reduction in diuretic dose, the clinical absence of right heart failure and echocardiographic documentation of no more than mild-to-moderate residual postoperative tricuspid

regurgitation. An unsatisfactory outcome was defined when either the primary or secondary end-points were recorded.

Descriptive statistics were the primary focus of this analysis. Numeric data were presented by the following descriptive statistics as most appropriate: mean, median, standard deviation, range, quartile 1, quartile 3 and interquartile range. Categorical data were presented by frequency tables (count and percentage).

Five categorical independent variables (atrial fibrillation, suture annuloplasty, ring annuloplasty, persistent postoperative pulmonary hypertension and severe residual postoperative tricuspid regurgitation) were assessed for association to the primary end-point using Pearson's Chi-Square test. A p value <0.05 was considered as statistically significant.

Three continuous variables (preoperative left ventricular ejection fraction, preoperative pulmonary artery systolic pressure and postoperative tricuspid transvalvular gradient) were also assessed for association to the primary end-point using the Independent Samples T-test. A p value <0.05 was considered as statistically significant.

In order to establish other factors associated with the development of the secondary end-point, Pearson's Chi-Square test was applied to 4 categorical independent variables (atrial fibrillation, suture annuloplasty, ring annuloplasty, and persistent postoperative pulmonary hypertension) with respect to the secondary end-point. A p value <0.05 was considered as statistically significant.

The Independent Samples T-test was used to investigate the relationship between each of 4 continuous variables (preoperative left ventricular ejection fraction, preoperative pulmonary artery systolic pressure and preoperative as well as the postoperative forward tricuspid transvalvular gradient) and the secondary end-point. A p value <0.05 was considered as statistically significant.

Exploratory inferential statistics such as Pearson's Chi-Square test, Paired-Samples T-test, Independent-Samples T-test, Kruskal-Wallis one-way analysis of variance or Wilcoxon signed-rank test were used to assess the association between variables.

SPSS version 21 (SPSS Inc., Chicago, Illinois) was used to analyse the data. A p value <0.05 was considered as statistically significant.

CHAPTER 4

RESULTS

Demographic Data

A total of 30 operations were performed in 30 patients between July 2003 and December 2011. The median age was 32.5 years. The majority of subjects (96.6%) were in New York Heart Association (NYHA) functional classes 3 and 4. The underlying aetiology was rheumatic heart disease in the entire study population. Five patients had undergone prior open surgical procedures for left-sided valvular heart disease. Refer to Table 1.

Table 1. Demographic profile (30 patients).

Age, years	median 32.5, IQR 32.0
Gender, n (%)	male=8 (26.7)
NYHA functional class, n (%)	
Class 1	0 (0.0)
Class 2	1 (3.3)
Class 3	16 (53.3)
Class 4	13 (43.3)
Rheumatic aetiology, n (%)	30 (100.0)
Atrial fibrillation/flutter, n (%)	14 (46.7)
Previous valve surgery, n (%)	5 (16.7)
Co-morbidity, n (%)	
Hypertension	4 (13.3)
Previous stroke	2 (6.7)

Abbreviations: IQR, interquartile range; NYHA, New York Heart Association.

Echocardiographic Data

All subjects had severe tricuspid regurgitation preoperatively secondary to left-sided valvular heart disease. Twenty-six subjects (86.7%) had mitral valve disease. The preoperative characterisation of tricuspid valve leaflet anatomy demonstrated normal leaflets in 19 patients (63.3%) and mixed-tricuspid valve disease in 11 patients (36.7%). The pulmonary artery systolic pressure was elevated in all subjects. The mean tricuspid annular diameter was 37.3±6.3mm. Nine subjects (30%) were identified preoperatively to have a forward gradient >2.0mm Hg across the tricuspid valve. The median left ventricular ejection fraction was 55.0% (interquartile range 15.0%). Twenty subjects (66.7%) had a left ventricular ejection fraction between 40 and 59%. In this subgroup 13 patients (65.0%) had mitral valve disease, of whom 5 had mitral stenosis (38.4%) and 2 had mitral regurgitation (15.4%). Refer to Table 2.

Table 2. Preoperative echocardiographic data (30 patients).

Left-sided valve pathology, n (%)	
Mixed-mitral valve disease	9 (30.0)
Predominant stenosis	5 (16.7)
Predominant regurgitation	4 (13.3)
Mitral stenosis	10 (33.3)
Mitral regurgitation	7 (23.3)
Aortic stenosis	1 (3.3)
Aortic regurgitation	3 (10.0)
Tricuspid valve anatomy, n (%)	
Normal leaflets	19 (63.3)
Mixed-tricuspid valve disease	11 (36.7)
Dilated right atrium, n (%)	30 (100.0)
Dilated right ventricle, n (%)	30 (100.0)
Median pulmonary artery systolic pressure, mm Hg	64.0, IQR 30.0
Pulmonary artery systolic pressure, n (%)	
30-39 mm Hg	0 (0.0)
40-59 mm Hg	12 (40.0)
>60 mm Hg	18 (60.0)
Tricuspid valve annular diameter, n (%)	
32-35mm	14 (46.7)
36-39mm	7 (23.3)
>40mm	9 (30.0)
Tricuspid valve gradient >2.0mm Hg, n (%)	9 (30.0)
Mean tricuspid valve annular diameter, mm	37.3±6.3
Mean left ventricular end diastolic dimension, mm	55.2±11.5
Mean left ventricular end systolic dimension, mm	40.0±9.5
Median left ventricular ejection fraction, %	55.0, IQR 15.0
Left ventricular ejection fraction, n (%)	
>60%	9 (30.0)
50-59%	11 (36.7)
40-49%	9 (30.0)
<20%	1 (3.3)

Abbreviations: IQR, interquartile range.

Surgical Procedures

All subjects had left-sided valve replacement as well as concomitant tricuspid valve procedures.

A total of 23 mitral valve replacements were performed. In addition, there was 1 aortic valve replacement, 4 double-valve replacements and 2 redo mitral valve replacement operations. Mechanical valves were implanted in 26 of the study patients (86.7%). The mechanical prostheses used comprised the Sorin Bicarbon (Sorin Biomedica, Saluggia, Italy), On-X (MCRI, Austin, Texas), Medtronic Advantage (Medtronic Inc, Minneapolis, Minnesota) and St Jude Regent valves (St Jude Medical Inc, St Paul, Minnesota). Bioprosthetic valve replacements were performed using the Medtronic Hancock 2 (Medtronic Inc, Minneapolis, Minnesota) and Carpentier-Edwards Perimount valves (Edwards Lifesciences, Irvine, California). Refer to Table 3.

Table 3. Distribution of implanted valve prostheses by left-sided procedure.

	MVR	AVR	DVR	redo MVR
Mechanical valves, n				
Sorin Bicarbon	1		1	
On-X	16	1	1	2
Medtronic Advantage	2			
St Jude Regent	1		1	
Bioprosthetic valves, n				
Medtronic Hancock 2	2		1	
Carpentier-Edwards Perimount	1			

Abbreviations: MVR, mitral valve replacement; AVR, aortic valve replacement; DVR, mitral and aortic valve replacement.

With respect to simultaneous tricuspid valve procedures, tricuspid valve repair was performed in 28 patients (93.3%). The remaining 2 patients underwent tricuspid valve replacement. Twenty-two subjects (73.3%) had a suture annuloplasty procedure (De Vega) and a ring annuloplasty was employed in 6 subjects (20.0%). In the latter group, the devices implanted were the Duran Ancore ring (Medtronic Inc, Minneapolis, Minnesota), the Carpentier-Edwards ring (Edwards Lifesciences, Irvine, California) and the Carbomedics ring (Sulzer Carbomedics, Austin, Texas). Medtronic Hancock 2 bioprostheses were implanted in the 2 patients who underwent tricuspid valve replacement. Refer to Table 4.

Table 4. Surgical procedures (30 patients).

Previous left-sided valve surgery, n (%)	
Mitral valve repair	1 (3.3)
Mitral valve replacement	3 (10.0)
Aortic valve replacement	1 (3.3)
Composite procedures, n (%)	
MVR, tricuspid suture annuloplasty	16 (53.3)
MVR, tricuspid ring annuloplasty	5 (16.7)
MVR, TVR	2 (6.7)
Redo MVR, tricuspid suture annuloplasty	2 (6.7)
DVR, tricuspid suture annuloplasty	3 (10.0)
DVR, tricuspid ring annuloplasty	1 (3.3)
AVR, tricuspid suture annuloplasty	1 (3.3)
Type of left-sided prosthesis used, n (%)	
Mechanical	
MVR	20 (66.7)
DVR	4 (13.3)
Redo MVR	2 (6.7)
Biological	
MVR	3 (10.0)
DVR	1 (3.3)
Type of tricuspid valve procedure, n (%)	
Tricuspid valve repair	
Suture annuloplasty	22 (73.3)
Ring annuloplasty	6 (20.0)
Tricuspid valve replacement	
Bioprosthetic	2 (6.7)
Type of tricuspid device used, n (%)	
Annuloplasty ring	
Carpentier-Edwards ring	2 (6.7)
Carbomedics ring	1 (3.3)
Duran ring	3 (10.0)
Prosthetic valve	
Medtronic Hancock 2	2 (6.7)

Abbreviations: MVR, mitral valve replacement; AVR, aortic valve replacement; DVR, mitral and aortic valve replacement; TVR, tricuspid valve replacement.

Operative Outcomes

Immediate Outcomes

There were 2 early deaths from cardiovascular causes in the study. One patient had intractable heart failure postoperatively resulting in a prolonged intensive care stay and demised on day 30. The immediate postoperative echocardiogram demonstrated an ejection fraction of 20% (preoperative ejection fraction 58%) with severe residual tricuspid regurgitation. The second patient exhibited a low cardiac output state immediately postoperatively and demised on day 2 prior to postoperative echocardiographic evaluation. The preoperative echocardiogram demonstrated normal tricuspid leaflet anatomy without a transvalvular gradient, an ejection fraction of 45%, a pulmonary artery systolic pressure of 45mm Hg and a tricuspid annular diameter of 39mm.

Left ventricular dysfunction was documented in 3 additional patients postoperatively. Refer to Table 5 for the relevant perioperative data.

Table 5. Echocardiographic and bypass parameters recorded for 5 patients with postoperative left ventricular dysfunction.

Left-sided valve pathology	Preoperative PAS (mm Hg)	Preoperative EDD (mm)	Preoperative EF (%)	Postoperative EF (%)	Cross-clamp time (min)	Outcome
Severe MR	44	60	60	30	46	Discharged day 23
Severe MR	84	71	55	30	67	Discharged day 21
Severe MR	41	69	58	20	48	Demised
Moderate MS, severe AR	85	41	57	18	96	Discharged day 116
Periprosthetic mitral valve leak	45	60	45	Not recorded	146	Demised

Abbreviations: EF, ejection fraction; EDD, end-diastolic dimension; PAS, pulmonary artery systolic pressure; MR, mitral regurgitation; MS, mitral stenosis; AR, aortic regurgitation.

Right heart failure was noted in 11 patients. Three of these patients had a preoperative tricuspid transvalvular gradient which was noted to resolve postoperatively. In 2 other patients without a preoperative transvalvular gradient, a postoperative transvalvular gradient was a new finding. Half the subjects with right heart failure postoperatively (54.5%) had a preoperative pulmonary artery systolic pressure of between 50-69mm Hg. In addition, half the subjects (54.5%) from the same subgroup had a preoperative tricuspid annular diameter between 32-35mm. Using the Independent Samples T-test, none of the following preoperative variables (tricuspid valve gradient, pulmonary artery systolic pressure and tricuspid annular diameter) were found to be statistically significant factors for the development of postoperative right heart failure.

One patient with a low preoperative ejection fraction (15%) demonstrated a postoperative ejection fraction of 35% with mild residual tricuspid regurgitation following aortic valve replacement and tricuspid suture annuloplasty. He had a prolonged hospital stay (74 days) due to cardiac failure and was in functional NYHA class 2 on discharge.

There were 2 subjects with a preoperative pulmonary artery systolic pressure >110mm Hg. One patient with a pulmonary artery systolic pressure of 113mm Hg underwent a mitral valve replacement and tricuspid suture annuloplasty resulting in moderate postoperative tricuspid regurgitation with a pulmonary artery systolic pressure of 57mm Hg and a left ventricular ejection fraction of 65%. He was in NYHA functional Class 3 when discharged on day 7. The patient with a pulmonary artery systolic pressure of 126mm Hg underwent a mitral valve replacement and tricuspid ring annuloplasty and demonstrated mild postoperative tricuspid regurgitation with a pulmonary artery systolic pressure of 64mm Hg and a left ventricular ejection fraction of 35%. He was in NYHA functional class 2 when discharged on day 79.

Intermediate Outcomes

At 6 weeks postoperatively, a forward gradient >2.0mm Hg was recorded across the tricuspid valve in 2 patients and in 2 patients a tricuspid valvular periprosthetic leak was observed. Of the 2 patients with a transvalvular gradient, 1 had an identifiable gradient preoperatively whilst 1 had a new gradient identified after tricuspid suture annuloplasty.

Three patients had a period of prolonged ventilation (>10 days) postoperatively. Four patients had a prolonged intensive care unit stay (>14 days) postoperatively. Thirteen

patients had a prolonged hospital stay (>30days) postoperatively. The median hospital stay was 23.0 days (interquartile range 29.0 days).

Other complications identified were deep sternal wound sepsis in 1 patient and pressure ulcers in 3 patients. Refer to Table 6.

Table 6. Operative outcomes.

Immediate outcomes, n (%)	
Early mortality	2 (6.6)
Left ventricular dysfunction	3 (10.0)
Cardiac failure	11 (36.7)
Intermediate outcomes, n (%)	
Residual TR at 6 weeks	
None	1 (3.3)
Mild	11 (36.7)
Moderate	5 (16.7)
Severe	8 (26.7)
Tricuspid valve gradient >2.0mm Hg at 6 weeks	2 (6.6)
Prolonged ventilation	3 (10.0)
Prolonged ICU stay	4 (1.3)
Deep sternal wound sepsis	1 (3.3)
Pressure ulcers	3 (10.0)
Prolonged hospital stay	13 (43.3)
Delayed outcomes, n (%)	
Primary end-point reached	
Cardiovascular death	6 (20.0)
Readmission for cardiac failure	4 (1.3)
Tricuspid valve reoperation	0 (0.0)
Secondary end-point reached	
Severe residual tricuspid regurgitation	8 (26.7)

Abbreviations: ICU, intensive care unit; TR, tricuspid regurgitation; IQR, interquartile range.

A statistically significant improvement ($p<0.001$) in NYHA functional class was documented in 24 subjects (80%) between the preoperative and 6-week postoperative NYHA functional class using the Wilcoxon signed-rank test. Descriptive analysis of NYHA functional class is represented in Table 7.

Table 7. Comparison of immediate outcomes at 6 weeks (27 patients) with baseline data (30 patients).

	Preoperative, n (%)	Postoperative, n (%)	p Value
NYHA Class 1	0 (0.0)	7 (23.3)	NA
NYHA Class 2	1 (3.3)	8 (26.7)	NA
NYHA Class 3	16 (53.3)	10 (33.3)	NA
NYHA Class 4	13 (43.3)	2 (6.7)	NA
Mean tricuspid annular diameter, mm	37.3±6.3	30.8±5.5	0.001
Mean pulmonary artery systolic pressure, mm Hg	67.0±21.6	49.7±12.1	0.001
Severe tricuspid regurgitation, n (%)	30 (100.0)	8 (26.7)	<0.001
Mean left ventricular ejection fraction, %	53.7±11.0	41.7±15.1	0.004

Abbreviations: NYHA, New York Heart Association; NA, not applicable.

The immediate echocardiographic outcome at 6 weeks was studied with respect to tricuspid annular diameter, transvalvular gradient, left ventricular ejection fraction, pulmonary artery systolic pressure and the presence of severe tricuspid regurgitation and compared to the preoperative data using the Paired-Samples T-test. There were significant reductions in the postoperative tricuspid annular diameter, pulmonary artery systolic pressure, incidence of severe tricuspid regurgitation and tricuspid transvalvular gradient. However, a significant deterioration in the postoperative ejection fraction was also observed. Refer to Table 7.

Delayed outcomes

The postoperative echocardiographic data at 1 year are presented in Table 8.

Table 8. Postoperative echocardiographic data at 1 year (21 patients).

Mean pulmonary artery systolic pressure, mm Hg	42.0±10.9
Pulmonary artery systolic pressure, n (%)	
<30mm Hg	3 (10.0)
30-39 mm Hg	7 (23.3)
40-59 mm Hg	10 (33.3)
>60 mm Hg	0 (0.0)
Mean tricuspid valve annular diameter, mm	33.7±4.6
Median tricuspid valve gradient >2.0mm Hg, n (%)	1.9, IQR 3.4
Median left ventricular end diastolic dimension, mm	52.2, IQR 8.0
Median left ventricular end systolic dimension, mm	37.0, IQR 3.0
Median left ventricular ejection fraction, %	46.0, IQR 15.0
Left ventricular ejection fraction, n (%)	
>60%	2
50-59%	6
40-49%	9
30-39%	1
20-29%	2

Primary End-point

The primary end-point was recorded in 10 patients (33.3%) at completion of the follow-up period comprising cardiovascular death (6 patients) and readmission for cardiac failure (4 patients). Tricuspid valve reoperation was not performed in this group during the study period.

In order to establish other factors associated with the development of the primary end-point, Pearson's Chi-Square test was applied to 5 categorical independent variables (atrial

fibrillation, suture annuloplasty, ring annuloplasty, persistent postoperative pulmonary hypertension and severe residual postoperative tricuspid regurgitation) with respect to the primary end-point. Persistent postoperative pulmonary hypertension was found to be the only statistically significant independent variable ($p<0.002$) associated with the primary end-point.

The Independent Samples T-test was used to investigate the relationship between each of 3 continuous variables (preoperative left ventricular ejection fraction, preoperative pulmonary artery systolic pressure and postoperative tricuspid transvalvular gradient) and the primary end-point. Only the preoperative pulmonary artery systolic pressure was found to have a statistically significant impact on the primary end-point (p 0.013).

Secondary End-point

The secondary end-point of severe residual postoperative tricuspid regurgitation was reached in 8 patients (26.7%) at completion of the follow-up period. Three of these patients had a forward transvalvular gradient >2.0mm Hg documented preoperatively. The relationship of the secondary end-point on the primary end-point was investigated by Pearson's Chi-Square test and found not to be statistically significant (p 0.149).

In addition, the effect of the severity of residual postoperative tricuspid regurgitation on the primary end-point was investigated using the Kruskal-Wallis one-way analysis of variance. No significant difference was observed amongst the 3 categories of residual postoperative tricuspid regurgitation on the primary end-point.

Table 9. Frequencies and percentages for variables assessed for association with the primary and secondary end-points.

	sample					
	Valid		Missing		Total	
	n	%	n	%	n	%
primary end point * AF	30	100.0%	0	0.0%	30	100.0%
primary end point * SA	30	100.0%	0	0.0%	30	100.0%
primary end point * SRTR	27	90.0%	3	10.0%	30	100.0%
primary end point * RA	30	100.0%	0	0.0%	30	100.0%
primary end point * severe TR	30	100.0%	0	0.0%	30	100.0%
secondary endpoint * AF	30	100.0%	0	0.0%	30	100.0%
secondary endpoint * SA	30	100.0%	0	0.0%	30	100.0%
secondary endpoint * SRTR	27	90.0%	3	10.0%	30	100.0%
secondary endpoint * RA	30	100.0%	0	0.0%	30	100.0%
secondary endpoint * severe TR	30	100.0%	0	0.0%	30	100.0%

Abbreviations: AF, fibrillation; SA, suture annuloplasty; SRTR, severe residual postoperative tricuspid regurgitation; RA, ring annuloplasty; TR, tricuspid regurgitation.

Persistence of severe postoperative tricuspid regurgitation

By use of the Independent Samples T-test, neither of the following preoperative categorical variables (pulmonary artery systolic pressure and tricuspid annular diameter) was found to have an impact on severe persistent postoperative tricuspid regurgitation. In addition, no association between the preoperative tricuspid leaflet anatomy and severe persistent postoperative tricuspid regurgitation was demonstrated using Pearson's Chi-square test.

In order to establish other factors associated with the development of the secondary end-point, Pearson's Chi-Square test was applied to 4 categorical independent variables (atrial

fibrillation, suture annuloplasty, ring annuloplasty, and persistent postoperative pulmonary hypertension) with respect to the secondary end-point. None of the listed variables were statistically significant.

The Independent Samples T-test was used to investigate the relationship between each of 4 continuous variables (preoperative left ventricular ejection fraction, preoperative pulmonary artery systolic pressure and preoperative as well as the postoperative forward tricuspid transvalvular gradient) and the secondary end-point. None of these variables were statistically significant with respect to the secondary end-point.

Ring annuloplasty vs suture annuloplasty on primary and secondary end-points

Using Pearson's Chi-Square Test, the association between the technique of annuloplasty and the primary and secondary end-points was investigated. Neither of the tricuspid repair techniques impacted on the primary or secondary end-points.

Outcome of tricuspid valve surgery in patients undergoing left-sided valve surgery

Analysis of surgical outcomes at 2 years as defined by the study protocol demonstrated a satisfactory outcome in 12 patients (40.0%) and an unsatisfactory outcome in 10 patients (33.3%). The remaining 8 patients were lost to follow-up.

Relationship between pulmonary hypertension and long-term surgical outcomes

The relationship between postoperative pulmonary hypertension and long-term outcomes in patients with surgically treated severe tricuspid regurgitation was examined using Pearson's

Chi-Square test in relation to the primary and secondary end-points. The presence of persistent postoperative pulmonary hypertension was found to be a statistically significant risk factor ($p<0.02$) for major adverse cardiovascular events (primary end-point). However, the presence of persistent postoperative pulmonary hypertension was not statistically significant with respect to the occurrence of severe residual postoperative tricuspid regurgitation (secondary end-point).

Follow-up

The median follow-up duration was 544.0 days (interquartile range 1357.0 days). Follow-up was complete in 16 patients (53.3%) and 8 patients (26.7%) were lost to follow-up (range 0-113 days).

There were 4 late deaths reported during follow-up excluding the 2 reported in-hospital deaths. One was due to a clotted mechanical mitral valve. In addition, 1 patient had a cerebrovascular accident, the mechanism of which was not established, and in whom the adequacy of anticoagulation was unknown.

Table 10 summarises the number of patients available for analysis at prescribed time-points.

Table 10. Analysis of follow-up at prescribed study intervals.

Follow-up interval	Total number of patients lost to follow-up	Total number of patients demised	Comments
6 weeks	2	2	2 in-hospital deaths
6 months	5	2	5 patients untraceable at 6 months
1 year	6	3	1 further death at 1 year, cause of death unknown but left ventricular dysfunction documented
2 years	8	6	3 further late deaths; cause of death: stroke, clotted mechanical valve and unknown 3 further patients untraceable at 2 years

Analysis of the diuretic dose at 2-year follow-up demonstrated an increased dose in 2 patients (6.7%), a decreased dose in 8 patients (26.7%) and an unchanged dose in 6 patients (20.0%).

A persistent forward transvalvular gradient >2.0mm Hg was observed in 4 patients (13.3%) at 2-year follow-up. The mean transvalvular gradient for the corresponding period was 3.8±2.16mm Hg. Of the original 9 patients with a preoperatively detectable gradient, 2 patients had a persistent gradient at 2 years postoperatively (numbers 1 & 2, Table 11) and the gradient was abolished in 6 patients. Furthermore, a postoperative gradient at 2 years was a new finding in 2 additional patients (numbers 3 & 4, Table 11).

Table 11. Clinical and echocardiographic characteristics of subjects with residual postoperative tricuspid transvalvular gradients at 2-year follow-up.

Patient	Postoperative TV gradient (mm Hg)	Postoperative NHYA class	Postoperative diuretic dose	Postoperative residual TR	Postoperative PAS (mm Hg)	Intraoperative valvular anatomy
1	2.6	2	Decreased	Severe	38	Normal leaflets
2	3.0	2	Increased	Severe	48	Normal leaflets
3	5.3	1	Decreased	Severe	57	Fusion of anterior and septal leaflets
4	5.9	2	Decreased	Mild	55	Mildly thickened leaflets

Abbreviations: TV, tricuspid valve; NYHA, New York Heart Association; TR, tricuspid regurgitation; PAS, pulmonary artery systolic pressure.

CHAPTER 5

DISCUSSION

This study shows that whilst the early results of surgery for functional tricuspid regurgitation are encouraging, there was a high prevalence (26.7%) of severe residual postoperative tricuspid regurgitation contributing to poor long-term outcomes.

Significantly, the study disproved the hypothesis that postoperative pulmonary hypertension is the major cause of persistence and exacerbation of tricuspid regurgitation even after successful left-sided valve surgery. We have shown that severe residual postoperative tricuspid regurgitation was not due to the presence of persistent postoperative pulmonary hypertension alone, but may be explained by several other factors. This finding is consistent with that of Matsuyama and colleagues who sought to identify predictors of residual tricuspid regurgitation after mitral valve surgery[24]. They suggest that several mechanisms may be responsible for the high prevalence of late tricuspid regurgitation including persistent pressure overload from pulmonary hypertension, right ventricular dysfunction, tricuspid annular dilatation and a postoperative increase in cardiac output which may inhibit the regression of tricuspid annular dilatation.

The major findings of this study may be summarised as follows: A statistically significant improvement in NYHA functional class was documented between the preoperative and 6-week postoperative exercise capacity. There was a significant reduction at 6 weeks in the postoperative tricuspid annular diameter, pulmonary artery systolic pressure, tricuspid regurgitation severity and tricuspid transvalvular gradient. In addition, there was a

significant deterioration in the postoperative ejection fraction. The primary end-point (death from a cardiovascular cause/the need for tricuspid valve reoperation/the presence of postoperative congestive cardiac failure requiring hospital admission) was recorded in 10 patients (33.3%) at completion of follow-up. Both, preoperative and persistent postoperative pulmonary hypertension were found to be statistically significant variables with respect to major adverse cardiovascular events (primary end-point). The secondary end-point (severe residual postoperative tricuspid regurgitation) was reached in 8 patients (26.7%) at completion of follow-up. There was no association between the secondary end-point and the development of major adverse cardiovascular events (primary end-point).

A further important finding of this study was that we found co-existent mixed-tricuspid valve disease in 36.7% of subjects. This is not surprising since this study population consisted of predominantly young patients with rheumatic valvular disease. The significance of this aetiology is that there is potential for organic tricuspid valve disease to be present preoperatively in the form of rheumatic involvement of the leaflets or commissures. This is highlighted by the development of a new postoperative gradient in 2 patients in the study sample. Of note is that the classical markers for organic valve disease (leaflet thickening, fusion, tethering, stiffness and failure of coaptation) may not always be discernible using conventional two-dimensional transthoracic echocardiography[12]. This idea is further explored by Henien and others, who contend that in patients with rheumatic mitral valve disease, organic tricuspid valve involvement is commoner than what may be apparent on routine transthoracic echocardiography[12]. Therefore, reliance on two-dimensional transthoracic echocardiography for assessment of valvular morphology may

compound the problem of non-recognition of a transvalvular gradient. In the absence of evaluation by three-dimensional echocardiography, it may be possible for organic tricuspid disease to remain unrecognised. The use of two-dimensional transthoracic echocardiography therefore represents a potential limitation of this study.

It may be inferred that in the subgroup with mixed-tricuspid valve disease, the significance of the forward transvalvular gradient in the presence of severe tricuspid regurgitation was not recognised at the time of surgical decision-making, hence the low rate of tricuspid valve replacement and a preference for tricuspid repair procedures. This serves to emphasise the importance of recognising the presence of a tricuspid transvalvular forward gradient, both, at initial echocardiographic evaluation as well as during preoperative and intraoperative evaluation. The presumption that the underlying tricuspid pathology is "functional" regurgitation carries a potential for non-recognition of organic disease of the tricuspid valve with resultant errors in surgical decision-making. In this context, it should be stated that the potential presence of a transvalvular forward gradient should be actively sought after, even in the presence what is ostensibly "functional" tricuspid regurgitation. Routine intraoperative use of transoesophageal echocardiography may reduce errors in assessment and also enhance the immediate results of tricuspid repair procedures.

Of greater concern, is the conclusion by Henein and others that rheumatic leaflet involvement contributes to severe tricuspid regurgitation occurring long after mitral valve surgery[12]. An additional concern is raised by Bernal and co-workers who observe that in patients with rheumatic valve disease, the durability of tricuspid valve repair is compromised by the active and progressive characteristics of the disease process[44]. As a consequence,

surgical techniques reserved for the management of functional tricuspid regurgitation may be erroneously applied to this group of patients who require tricuspid valve replacement instead, resulting in unpredictable outcomes. Bernal and others underscore this point with their conclusion that the results of tricuspid valve repair for organic disease are less favourable than those of repair procedures for functional tricuspid regurgitation[62].

The fact that almost half the study patients had atrial fibrillation preoperatively is consistent with the finding that atrial fibrillation and tricuspid annular dilatation are directly related to left atrial dilatation on the basis of increased left atrial pressure[5]. However, in our study, the presence of atrial fibrillation was shown to have no correlation with severe residual postoperative tricuspid regurgitation (secondary end-point) or the primary end-point (death from a cardiovascular cause/the need for tricuspid valve reoperation/the presence of postoperative congestive cardiac failure requiring hospital admission). This contrasts with other reports where the presence of atrial fibrillation was demonstrated to be a risk factor for residual tricuspid regurgitation[24,26]. Similarly, Song and co-workers found atrial fibrillation to be an independent risk-factor for the development of late severe tricuspid regurgitation[26]. Fuster et al suggest that routine surgical elimination of atrial fibrillation could significantly reduce the incidence of late severe tricuspid regurgitation. The fact that surgical ablation for atrial fibrillation was not performed in this group may represent a further shortcoming of this study.

The distribution of tricuspid valve repair procedures in this study demonstrated a bias towards suture annuloplasty (73.3%) versus ring annuloplasty (20.0%). The choice between suture annuloplasty and ring annuloplasty may be possibly explained by a procedure

selection bias amongst the participating surgeons. Potential factors include personal preference, previous surgical experience and performance bias. The suture annuloplasty technique is less expensive, simpler to perform and less time consuming but its inherent drawback is a lack of reproducibility when exact quantitative repair techniques are not employed[33,63]. As a result, surgical outcomes with this technique are less predictable. In view of the published superiority of results with ring annuloplasty techniques, it would be desirable for the available clinical evidence to prevail over personal preference in the selection of tricuspid repair procedures[48,49,50,51,52].

The use of mechanical valves predominated in the left-sided valve replacement procedures, but only biological valves were implanted in the tricuspid position in this study population. Valve choice is influenced by patient and prosthesis characteristics. This study sample consisted of a relatively young population (median age 32.5 years) similar to the cohort described by Kaplan et al wherein mechanical valve choice in the tricuspid position was based on favourable haemodynamic characteristics and durability[53]. Similarly, Scully and others recommend a mechanical prosthesis in the tricuspid position in younger patients also receiving mechanical valves on the left-side necessitating anticoagulation therapy[54]. The use of bioprostheses in the tricuspid position is tempered by concerns over long-term durability and thrombogenicity. The observed preference for a tricuspid bioprosthesis in our study population may be explained by concerns over poor compliance with anticoagulation therapy and monitoring in this study population, with the attendant risk of mechanical tricuspid valve thrombosis.

In 36.7% of subjects, right heart failure was documented postoperatively at 6 weeks. It is relevant to note that Guenther and others propose that this patient cohort reflects an advanced stage of heart disease often accompanied by severe right ventricular dysfunction[39]. It may be surmised that postoperative right heart failure may be a continuum of preoperative right ventricular dysfunction not immediately remediable by surgical intervention in the face of elevated pulmonary artery pressure. In this study, none of the following preoperative variables: tricuspid valve gradient, pulmonary artery systolic pressure and tricuspid annular diameter were found to be causally related to this complication. Possible reasons for this may include the relatively small sample size studied, a delayed reduction in pulmonary artery pressure and persistence of right ventricular dysfunction.

Severe residual tricuspid regurgitation occurred in 26.7% of subjects at 6 weeks postoperatively. This figure appears to be unexpectedly high given the anticipation that tricuspid regurgitation would regress postoperatively as pulmonary artery pressure diminishes. The fact that the entire subgroup with severe residual tricuspid regurgitation underwent tricuspid suture annuloplasty is noteworthy. The high observed incidence of severe postoperative tricuspid regurgitation may possibly be explained by the following: the sequelae of rheumatic leaflet disease[12], inefficacy of the suture annuloplasty procedure, tricuspid repair techniques being applied inappropriately in the presence of mixed-tricuspid valve disease, the presence of tricuspid leaflet tethering[28] or atrial fibrillation[24,26] and inadequate preservation of the mitral subvalvar apparatus[27].

The observation that a statistically significant decline in postoperative left ventricular function occurred in this study is remarkable. Inadequate myocardial preservation may be a possible contributing factor. However the interplay between systolic wall stress and myocardial fibre shortening may account for the diminished ejection fraction more convincingly. In decompensated mitral regurgitation, reduced ejection fraction may occur as a result of decreased myocardial fibre shortening in response to increased systolic wall stress following mitral valve replacement. In compensated mitral regurgitation, despite a reduced afterload following mitral valve replacement, the ejection fraction may diminish due to disrupted mitral annular and subvalvar function.

The high observed incidence of severe residual postoperative tricuspid regurgitation highlights the issue of tricuspid repair failure. McCarthy et al documented a 14% incidence of residual tricuspid regurgitation early postoperatively for all types of annuloplasty. They concluded that the severity of preoperative tricuspid regurgitation determined the risk of repair failure within the first 6 months of surgery[57]. This conclusion is reinforced by Kuwaki and others who found that the severity of preoperative tricuspid regurgitation predicted early residual tricuspid regurgitation[58]. Significantly, severe preoperative functional tricuspid regurgitation was an inclusion criterion for this study, therefore the high observed incidence of severe residual tricuspid regurgitation may be a self-fulfilling phenomenon based on pre-selection.

Surgical decision-making in the presence of functional tricuspid regurgitation is challenged by the uncertainty whether this phenomenon will regress or progress after surgery if left untreated. However, the scientific literature identifies some predictors of residual tricuspid

regurgitation after left-sided surgery, the cognisance of which may influence surgical strategies. These factors are: a left atrial diameter >60mm, atrial fibrillation, preoperative tricuspid annular dilatation, age, female gender, rheumatic aetiology, failure to preserve the mitral subvalvar apparatus, failure to surgically eliminate atrial fibrillation and preoperative tricuspid leaflet tethering[24,25,26,27,28].

In this study, there was no statistical relationship between the presence of severe residual postoperative tricuspid regurgitation and the following variables: atrial fibrillation, suture annuloplasty, ring annuloplasty, persistent postoperative pulmonary hypertension, left ventricular ejection fraction, preoperative pulmonary artery systolic pressure, preoperative tricuspid leaflet anatomy, tricuspid annular diameter and postoperative tricuspid transvalvular gradient. This partially contradicts the surgical literature where atrial fibrillation[24,26] and preoperative tricuspid annular dilatation[25] have already been demonstrated to be related to the occurrence of residual postoperative tricuspid regurgitation. The relatively small sample size may account for our finding.

With regard to the primary end-point, which was documented in 33.3% of subjects, the absence of tricuspid valve reoperation in this study was significant. It may be postulated that subjects either demised prior to repeat surgery, or that their clinical condition did not permit reoperative surgery. In a series of patients undergoing tricuspid valve reoperation after previous tricuspid repair, Bernal et al found that reoperation was indicated in 33.8% of patients due to progression of valve disease and in 14.9% of patients for early failure of tricuspid valve repair[61]. Their high recorded incidence of reoperation may be due to the fact

that the reported mean interval between primary repair and reoperation was 8.2 years, a time-frame far exceeding the follow-up period in our study.

In this study, the primary end-point of major adverse cardiovascular events (death from a cardiovascular cause/the need for tricuspid valve reoperation/the presence of postoperative congestive cardiac failure requiring hospital admission) was found to have no statistical association with the following variables: atrial fibrillation, suture annuloplasty, ring annuloplasty, preoperative left ventricular ejection fraction, postoperative tricuspid transvalvular gradient and severe residual postoperative tricuspid regurgitation. This finding differs from published reports where preoperative left ventricular dysfunction[45] and non-use of an annuloplasty ring[44,48,49] have been shown to be related to major adverse cardiovascular events. However, in this study the preoperative pulmonary artery systolic pressure and persistence of postoperative pulmonary hypertension were found to be associated with major adverse cardiovascular events; the former being consistent with the surgical literature[46].

The relationship between ring annuloplasty and suture annuloplasty on the primary and secondary end-points was investigated but neither of these repair techniques made a statistically significant impact on the 2 end-points. It is possible that the small sample size may have masked the true influence of suture annuloplasty on the end-points in this study. These findings contrast with the surgical literature which indicates that ring annuloplasty is the superior form of treatment for patients with functional tricuspid regurgitation[48,49,51]. In a multivariate analysis, Tang and others showed that the use of an annuloplasty ring was an independent predictor of long-term survival[48]. They also illustrated better event-free

survival, freedom from recurrent tricuspid regurgitation and fewer tricuspid reoperations in the ring annuloplasty group. Guenther and others affirm this with evidence that ring annuloplasty is associated with improved survival and a lower reoperation rate[49]. Seitelberger et al report that survival in the suture annuloplasty group was lower during long-term follow-up[50]. They also found a greater tendency for recurrent tricuspid regurgitation as well as a higher rate of tricuspid valve reoperation in the suture annuloplasty group.

Surgical outcomes were analysed by defined criteria described in the study protocol. A satisfactory outcome was demonstrated in only 40% of patients. A major contributing factor to unsatisfactory outcomes was the occurrence of severe residual tricuspid regurgitation at long-term follow-up. We could not make any inferences from this data because of the small sample size and the loss of 26.7% of subjects to follow-up. However, it may be postulated that outcomes could be improved by the selection of surgical strategies which result in a lower incidence of severe residual postoperative tricuspid regurgitation, namely the routine use of preoperative three-dimensional and intraoperative transoesophageal echocardiography and wider application of ring annuloplasty repair as well as surgical ablation of atrial fibrillation.

The limitations identified in this study are related to study design. It is a retrospective, observational, non-randomised study with a potential for procedure selection bias. The relatively small sample size was a recognized limitation of this study with respect to statistical power. Also undermining statistical power was the fact that 26.7% of patients were lost to follow-up. The use of two-dimensional transthoracic echocardiographic

evaluation, failure to elucidate preoperative tricuspid leaflet tethering and non-use of intraoperative transoesophageal echocardiography as well as failure to surgically ablate atrial fibrillation may be additional study limitations. A follow-up period of 2 years appears to be insufficient compared to the literature, where long-term follow up has been reported in the analysis of outcomes. In addition, a control group would have been desirable. However, this subset would ideally have comprised patients with severe functional tricuspid regurgitation undergoing left-sided valve surgery, in which tricuspid regurgitation was not addressed at the time of left-sided valve surgery. Based on currently available evidence, failure to correct severe tricuspid regurgitation simultaneously would represent a departure from acceptable standards of contemporary surgical practice and may well be unethical[18,23,24].

CHAPTER 6

CONCLUSION

This study examined the results of simultaneous tricuspid valve surgery for severe functional tricuspid regurgitation in patients undergoing left-sided surgery for rheumatic valvular disease.

Tricuspid valve surgery was associated with a significant improvement in the following parameters at 6 weeks postoperatively: NYHA functional class, tricuspid annular diameter, pulmonary artery systolic pressure, severity of tricuspid regurgitation and tricuspid transvalvular gradient. Despite the encouraging immediate results of tricuspid valve surgery, the development of delayed severe residual postoperative tricuspid regurgitation unrelated to traditional risk factors may serve to diminish surgical enthusiasm for tricuspid valve repair in rheumatic valvular disease.

The study hypothesis that preoperative pulmonary hypertension is associated with persistence and exacerbation of tricuspid regurgitation even after successful left-sided valve surgery was disproven. We have shown that the presence of persistent postoperative pulmonary hypertension was not a major determinant of severe residual postoperative tricuspid regurgitation although it was associated with the occurrence of major adverse cardiovascular events (primary end-point).

There were no identifiable predictors for the development of severe residual postoperative tricuspid regurgitation in this study and no relationship was demonstrated between the

development of severe residual postoperative tricuspid regurgitation and major adverse cardiovascular events (primary end-point).

The underlying aetiology of left-sided valve pathology was rheumatic heart disease in the entire study population. The preoperative evaluation of tricuspid regurgitation in these subjects suggested functional tricuspid regurgitation, however we have shown that rheumatic involvement of the tricuspid valve carried a potential for non-recognition of morphological abnormalities using standard two-dimensional transthoracic echocardiography. This condition may also contribute to severe tricuspid regurgitation long after left-sided valve surgery. Undiagnosed organic tricuspid valve disease may result in inappropriate selection of tricuspid valve repair techniques over tricuspid valve replacement procedures. The results of tricuspid valve repair for organic disease are less favourable than those of repair procedures for functional tricuspid regurgitation, therefore it is imperative that organic tricuspid valve disease is elucidated preoperatively in order to dictate the most appropriate surgical intervention.

There appeared to be a procedure selection bias towards tricuspid suture annuloplasty in the study, despite the published superiority of results obtained using the ring annuloplasty technique. However, we could not demonstrate an association between the technique of tricuspid valve repair and the occurrence of major adverse cardiovascular events (primary end-point), or the development of severe residual postoperative tricuspid regurgitation (secondary end-point).

This study shows that persistence of severe tricuspid regurgitation occurs in a substantial proportion of patients undergoing tricuspid valve repair, compromising surgical outcomes.

Analysis of the 2-year follow-up data demonstrated a satisfactory surgical outcome in only 40% of the study population, the outcome being adversely influenced by the occurrence of severe residual postoperative tricuspid regurgitation (secondary end-point). Multiple factors may be implicated, including the choice of annuloplasty technique and the sequelae of ongoing rheumatic tricuspid valve disease. Outcomes may therefore be markedly influenced by the technique of perioperative imaging and the choice of annuloplasty procedure.

This study suggests that the management of patients with functional tricuspid regurgitation of rheumatic aetiology should encompass surgical strategies which result in a lower incidence of severe residual postoperative tricuspid regurgitation, namely the routine use of preoperative three-dimensional and intraoperative transoesophageal echocardiography to comprehensively delineate valve morphology, as well as wider application of ring annuloplasty repair techniques.

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