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Risk factors of tricuspid insufficiency after cardiac transplantation

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Abstract

Background

The occurrence of tricuspid insufficiency (TI) is common after orthotopic heart transplantation (HTx) with a prevalence up to 98 %. Although it is normally asymptomatic, it can sometimes be serious and lead to mortality. Several studies have attempted to study risk factors for the development of TI. However, there is no consistency between these studies in reporting risk factors. The study presented here is unique, since it analyzes most of the possible variables influencing TI after HTx, identifies possible risk factors responsible for TI development and progression, identifies the mechanisms of TI occurrence and suggests strategies to prevent TI development after HTx.

Methods

Tricuspid insufficiency was identified in 857 of 1515 patients who underwent HTx in the years 1986-2010, survived at least 12 months and had echocardiographic assessments. The risk factors that can influence tricuspid insufficiency were statistically analyzed in a group of 152 patients at the middle of follow-up time. The group was identified as a representative group. The patients of the representative group were subdivided into two groups according to the severity of TI: patients with TI grade ≤ 2 and those with TI grade >2.

Results

No significant differences between the groups in terms of recipient gender, basic disease, recipient weight, recipient body mass index, recipient body surface area, pre-operative pulmonary arterial pressure, donor organ ischemia time, donor gender, donor age, donor height, donor weight, donor body mass index (BMI), donor body surface area (BSA), chest X-ray thorax width, chest X-ray heart width, chest X-ray thorax/heart ratio, highest rejection grade on biopsy or degree of cardiac allograft vasculopathy (CAV) were found.

In an univariable analysis, study variables such as age of recipient ($p=0.027$), donor to recipient right atrium anterior wall ratio ($p<0.001$) , tricuspid annulus anterior to septal leaflet excursion ratio ($p=0.001$), dialysis ($p=0.026$) and total biopsy number ($p=0.003$) showed significant differences and the variables height of recipient ($p=0.080$), BMI donor to BMI recipient ratio ($p=0.080$) and number of biopsies with more than moderate grade ($p=0.067$) showed a trend towards significance in the development of severe TI after HTx. In multivariable analysis, we found an independent significant association between tricuspid insufficiency after HTx and donor to recipient right atrium anterior wall ratio, number of biopsies and dialysis. Moderate to severe and severe TI have no significance for mortality after HTx.

Conclusion

From the present study, it is evident that donor to recipient right atrium front wall ratio, number of biopsies, and dialysis act as major risk factors for tricuspid insufficiency after orthotopic heart transplantation. This shows that preserving atrial geometry, decreasing biopsy number and preventing functional tricuspid insufficiency are essential for freedom from further progression of tricuspid insufficiency after cardiac transplantation. Therefore, it is important to utilize the appropriate surgical technique, intensified ultrafiltration for patients on dialysis and non-invasive diagnostic modalities to reduce the number of endomyocardial biopsies (EMB) in order to prevent TI after HTx.

Abstract

Hintergrund

Eine Trikuspidalinsuffizienz (TI) tritt häufig nach orthotoper Herztransplantation (HTx) auf und wird mit einer Prävalenz von bis zu 98 % angegeben. In der Regel asymptomatisch kann sie in Einzelfällen einen gravierenden Verlauf annehmen bis hin zur Mortalität. In zahlreichen Studien ist der Versuch unternommen worden, Risikofaktoren für die Entwicklung von TI zu untersuchen. Zwischen diesen Studien gibt es in der Berichterstattung von Risikofaktoren jedoch keine Konsistenz. Die hier vorgelegte Studie ist einmalig, da sie mögliche Variablen analysiert, welche einen Einfluss auf TI nach HTx haben können, mögliche Risikofaktoren ermittelt, die für die Entwicklung und das Fortschreiten von TI verantwortlich sein können, Mechanismen identifiziert, die am Auftreten von TI beteiligt sind und Strategien zur Prävention von TI nach HTx vorschlägt.

Methoden

Bei 857 von 1515 Patienten, die sich in den Jahren 1986 bis 2010 einer HTx unterzogen, mindestens 12 Monate überlebt haben und für die eine echokardiographische Evaluation vorlag, wurde eine Trikuspidalinsuffizienz identifiziert. Für eine Gruppe von 152 Patienten wurden die Risikofaktoren, welche die TI beeinflussen können, in der Mitte des Follow-Up statistisch analysiert. Diese Gruppe konnte als repräsentativ identifiziert werden und ihre Patienten nach Schweregrad der TI in zwei Gruppen unterteilt: Patienten mit TI-Grad ≤ 2 und mit TI-Grad > 2.

Ergebnisse

Es wurde zwischen beiden Gruppen kein signifikanter Unterschied festgestellt hinsichtlich Geschlecht, Grunderkrankung, Gewicht, Körpermassindex (BMI) oder Körperoberfläche (BSA) des Empfängers, präoperativem pulmonalarteriellem Druck und Ischämiezeit des Spenderorgans, Geschlecht, Alter, Körpergröße, Gewicht, BMI oder BSA des Spenders, Breite des Thorax und Herz-Thorax-Quotient bei Röntgenaufnahme, sowie höchstem Abstoßungsgrad bei Biopsie oder vaskulärer Reaktion.

Die univariate Analyse zeigte bei Studienvariablen wie Alter des Empfängers ($p=0.027$), Spender-/Empfänger-Verhältnis der rechtsatrialen Vorderwand ($p<0.001$), Exkursionsverhältnis vom vorderen zum septalen Tricuspidalannulus ($p=0.001$), Dialyse ($p=0.026$) sowie Gesamtzahl der Biopsien ($p=0.003$) signifikante Differenzen und bei den Variablen Körpergröße des Empfängers ($p=0.080$), Verhältnis zwischen Spender-BMI und Empfänger-BMI ($p=0.080$) und Anzahl der Biopsien mit einem Grad höher als mittelgradig ($p=0.067$) eine Tendenz zur Signifikanz in der Entwicklung einer schweren TI nach HTx. Die multivariate Analyse zeigte eine unabhängige signifikante Assoziation zwischen Trikuspidalinsuffizienz nach HTx und Spender-/Empfänger-Verhältnis der rechtsatrialen Vorderwand, der Biopsien-Anzahl und der Dialyse. Moderate bis schwere und schwere TI zeigten keine Signifikanz im Hinblick auf die Mortalität nach HTx.

Schlußfolgerung

Anhand der vorliegenden Studie wird deutlich, dass das Spender-/Empfänger-Verhältnis der rechtsatrialen Vorderwand, Biopsie-Anzahl und Dialyse die Hauptrisikofaktoren für Trikuspidalinsuffizienz nach orthotoper Herztransplantation sind. Dies zeigt, dass die Erhaltung der atrialen Geometrie, eine Reduzierung der Biopsie-Anzahl und die Vorbeugung von funktionaler Trikuspidalinsuffizienz essentiell sind, um ein weiteres Fortschreiten von TI nach Herztransplantation zu verhindern. Die Nutzung der geeigneten chirurgischen Technik, eine intensivierte Ultrafiltration bei Dialysepatienten und nicht-invasive diagnostische Verfahren sind wichtig, um die Zahl der Endomyokardbiopsien zu reduzieren und so eine TI nach HTx zu verhindern.

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Abbreviations and acronyms

AB0   AB zero

ACR   Acute cellular rejection

AIDS   Acquired immune deficiency syndrome

ATG   Anti-thymocyte globulin

AV   Atrioventricular

BMI   Body mass index

BSA   Body surface area

BW   Body weight

CAD   Coronary artery disease

CAV   Cardiac allograft vasculopathy

CI   Confidence interval

CPB   Cardiopulmonary bypass

CT   Computed tomography

D/R   Donor to recipient

DCM   Dilative cardiomyopathy

DHZB   Deutsches Herzzentrum Berlin

EMB   Endomyocardial biopsy

FTV   Flail tricuspid valve

HF   Heart failure

HIV   Human immune deficiency virus

HLA   Human leukocyte antigen

HTx	Heart transplantation (orthotopic)
IMEG	Intra-myocardial electrogram
ISHLT	International Society for Heart and Lung Transplantation
IVC	Inferior vena cava
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
OHD	Organic heart disease
PAP	Pulmonary artery pressure
PVR	Pulmonary vascular resistance
RA	Right atrium
RV	Right ventricle
RVEF	Right ventricular ejection fraction
SD	Standard deviation
SPAP	Systolic pulmonary artery pressure
SPSS	Statistical Products and Services Solutions
SVC	Superior vena cava
TI	Tricuspid insufficiency
TV	Tricuspid valve
VO_2 max.	Maximal oxygen consumption

1 Introduction

1.1 Background

Tricuspid insufficiency (TI) is a common valvular abnormality after orthotropic heart transplantation (HTx) with an incidence up to 98%, depending on definition of significant insufficiency[1]. Post-transplant TI is a dynamic illness and its occurrence and severity have been found to increase with time [2, 3]. TI has been associated with an increase in mortality and morbidity[4, 5]. High-grade TI has been identified to have an impact on right-sided heart failure and to produce symptoms such as oedema in the lower limbs, fatigue, and reduced tolerance of exertion, correlating with hepatomegaly and jugular venous distension[6-8,9]. Such complex conditions are refractory to medical management and hence TI should be treated with surgical methods[2]. Surgical management of TI after HTx consists of tricuspid valve annuloplasty or valve replacement[10-13].

The etiology of TI after HTx is still an open question. The mechanism behind its development can principally be divided into anatomic and functional. Functional TI is caused by geometric distortion or dilatation of the atrio-ventricular annular ring and valve leaflet malcoaptation[3, 14-16]. The regurgitant jet, seen on echocardiography, can be central or eccentric, depending on the pathology. Anatomic TI is caused by a torn leaflet, ruptured chordae, excessive leaflet motion or degeneration of the valve apparatus[17]. Based on the time of occurrence, it can be divided into early or late. Early TI has been correlated with preoperatively raised transpulmonary gradient, elevated pulmonary vascular resistance, allograft rejection and geometric distortion of the annular ring at the time of transplantation[15, 18]. Risk factors for late TI are the number of biopsies, number of rejection episodes of grade ≥ 2 and surgical technique[18].

1.2   Cardiac transplantation

1.2.1   History

The first reported successful experimental orthotopic cardiac transplantation was done in 1960 by Lower and Shumway in Stanford, California[19]. Dr. Christiaan Barnard performed the first successful human to human transplantation on December 3, 1967 in Cape Town, South Africa[20]. After successful cardiac transplantation by Barnard, clinical cardiac transplantation was started in many cardiac surgical centers worldwide, but the 1-year survival remained low[21]. Monitoring of cardiac allograft rejection became feasible after the introduction of transvenous endomyocardial biopsies by Philip Caves in 1973[22]. Years later, in 1981, the immunosuppressive agent was taken from the fungus-like *Tolypocl adium inflatum gams* and cyclosporine A was introduced; this was the next milestone for successful cardiac transplantation[23].

1.2.2   Preoperative considerations

Cardiac transplantation is surgical therapy used in patients with end-stage heart disease. The indication criterion for transplantation is low prognosis for 1-year survival, which can be determined by predictors of poor prognosis such as reduced ejection fraction, low VO_2max, arrhythmias, elevated capillary wedge pressure, high plasma or epinephrine concentration, renin activity and N-terminal pro-brain natriuretic peptide (NT-proBNP)[8, 24-28].

Absolute contraindications for heart transplantation are fixed pulmonary hypertension and systemic disease with poor prognosis such as neoplasm, HIV/AIDS, SLE, or irreversible renal or hepatic dysfunction. Some of the potential contraindications are chronic obstructive pulmonary disease, diabetes mellitus with end-organ damage, peripheral vascular disease, active peptic ulcer, severe osteoporosis, non-cardiac atherosclerosis and diverticulitis[29, 30].

The donor is selected only after completion of diagnosis of brain death and collection of information regarding age, height, weight, gender, cause of death, routine laboratory tests (AB0, HIV, HBV, HCV), electrocardiogram, chest roentgenogram, arterial blood gases, echocardiogram, pulmonary artery catheter evaluation and coronary angiography [31]. At the

time of organ procurement, the heart is visually inspected and palpated to check its anatomy and function and absence of infarction and valvular or coronary pathology.

AB0 group compatibility and immunologic compatibility are studied for donor recipient matching. Immunologic compatibility studies include: human leukocyte antigen (HLA) typing, white cell antibody screen, and lymphocyte cross match. The lymphocyte cross match is performed if the recipient has positive results of screening for antibodies or if screening has not been done. HLA matching is not performed in thoracic organ transplantation due to the ischemic time limits[21]. Cardiac ischemic time is the time required from clamping of the donor aorta until opening of the clamp in the recipient after the donor heart been transplanted. Further, patient body size is also important for this matching. A large-framed donor is favorable for patients with higher pulmonary artery pressure (PAP) to reduce the risk of right ventricular failure[2].

1.2.3 Operative technique

Procurement of the donor heart is usually performed during multi-organ retrieval. Firstly, a long midline incision is made from the the jugulum to the pubis. Median sternotomy is carried out and the pericardium is longitudinally incised. The heart is then inspected for any evidence of injury, cardiac disease or congenital anomalies. The superior and inferior vena cava is encircled and the aorta is mobilized. A purse string suture for the cardioplegic solution is placed. Before the cardiectomy, heparin is administered, the superior vena cava (SVC) is distally ligated. The inferior vena cava (IVC) is divided just proximal to the diaphragm. The aorta is occluded and cardioplegic solution is infused. The right superior pulmonary vein is incised, permitting unloading of the heart. The right pulmonary veins are divided at the pericardial reflection. After retraction of the heart to the right and superiorly, the left pulmonary veins are also transected. The aorta is transected at the origin of the brachiocephalic artery and then the right and left pulmonary arteries are also transected. The superior vena cava is divided at the pericardial reflection. After examination of the allograft for valve abnormalities and patent foramen ovale, it is placed in a sterile container for transport.

The recipient operation setup is similar to the setup for other open heart operations. Median sternotomy is performed. The aorta is cannulated as distal as possible. The vena cavae are also cannulated as distally as possible and caval tapes are placed.

The recipient cardiectomy is usually timed so that it is finished at the time that the donor heart arrives. Cardiopulmonary bypass is initiated. After the aorta is cross-clamped and the caval snares are tightened, the aorta and the pulmonary artery are separated and the interatrial groove is prepared. The great vessels are divided. Recipient cardiectomy is made by incision in the right and left atrium along the atrioventricular groove for the standard technique and both VCS and VCI are divided just at the cavo-atrial junction for the bicaval technique.

For the standard technique, the left atrial anastomosis is begun at the base of the left atrial appendage adjacent to the left superior pulmonary vein. The ends of the suture line are joined in the middle of the interatrial septum. After left atrial anastomosis, a right atrial incision is made from the IVC toward the right atrial appendage. The right atrium (RA) of the donor is anastomosed to the RA of the recipient, and the pulmonary trunk and aorta are anastomosed end to end.

For the bicaval technique, left atrial anastomosis is performed as in the standard technique and IVC and superior vena cava are anastomosed end to end. Transplantation is completed with anastomosis of the pulmonary trunk and aorta.

1.2.4 Postoperative care

Postoperative care after HTx is similar to that of any other patients after open heart surgery, with some special considerations. Donor heart function can be transiently depressed because of total denervation or prolonged ischemic time [32, 33]. Usually, inotropic support is needed for 2 to 5 days. Cardiac denervation can result in a reduction of the heart rate which is essential in maintaining adequate cardiac pump function. The heart rate can be maintained with a temporary pacemaker or chronotropic catecholamines[33]. Failure of the right ventricle (RV) can occur due to elevated pulmonary vascular resistance. It remains a leading cause of early mortality. Management includes inhalation of nitric oxide and therapy with vasodilators such as nitroglycerin, nitroprusside, prostaglandin E1 or prostacyclin[34].

Immunosuppressive therapy is important in perioperative and postoperative management to avoid rejection of the donor heart by the immune system of the recipient. The usual protocols include corticosteroids, calcineurin inhibitors and antimetabolic or antiproliferative agents. Some centers use also antilymphocyte antibodies. Corticosteroids decrease circulating lymphocytes, macrophage function and production of y-interferon and interleukins. Calcineurin inhibitors such as cyclosporine A, tacrolimus, rapamycin or everolimus prevent production and release of interleukin-2. Immunosuppressive agents such as azathioprine, methotrexate and mycophenolate mofetil act by inhibiting purine biosynthesis. Everolimus antilymphocyte antibodies such as antithymocyte globulin, OKT 3 or the interleukin-2 receptor blockers daclizumab and basiliximab act against the T-cells or block receptors on T-cells and are used as induction therapy[21].

Cardiac rejection is an immunologic host response to foreign cells that causes cellular infiltration of the myocardium and as a result potentially myocyte death. Although there are many non-invasive and alternative diagnostic methods such as non-invasive rejection monitoring by intramyocardial electrogramm (IMEG) and echocardiography, the endomyocardial biopsy (EMB) is still considered the 'gold standard' in most centers. During biopsy five or seven specimens are retrieved under fluoroscopic control from the intraventricular septum near the apex. Complications of EMB include carotid puncture, pneumothorax, arrhythmias, right ventricular perforation and injury of the tricuspid valve[35-39]. Endomyocardial biopsy is graded using the International Society for Heart and Lung Transplantation nomenclature adopted in 1990 and revised in 2005[40-42]:

Grade 0 — no rejection

Grade 1 R, mild — interstitial and/or perivascular infiltrate with up to one focus of myocyte damage

Grade 2 R, moderate — two or more foci of infiltrate with associated myocyte damage

Grade 3 R, severe — diffuse infiltrate with multifocal myocyte damage, with or without edema, hemorrhage, or vasculitis

Grade 1 R includes grades 1A, 1B, and 2 in the 1990 system; grade 2 R was grade 3A; and grade 3 R was grades 3B and 4. Therapy of acute rejection includes high dosage corticosteroids and if necessary administration of cyclosporine or ATG[21].

The major limitations to survival in the early post-transplant period are nonspecific graft failure, multi-organ failure, acute rejection, and infection. Beyond the first year, cardiac transplant vasculopathy is among the top three causes of death, after malignancy, as shown in the reports of the Registry of the International Society of Heart and Lung Transplantation[43]. It is a progressive form of atherosclerosis and is characterized by concentric fibrous intima of the coronary vessels[44]. Diagnosis can be made by using right ventricular endomyocardial biopsy, angiography, intravascular ultrasonography, and non-invasive examinations such as dobutamine stress echocardiography, CT and MRI[45]. Stenotic microvasculopathy demonstrated by stenotic wall thickening is a prognostic factor for long-term survival and associated with decreased freedom from fatal events[46]. Other complications are infections, renal dysfunction, hypertension and malignancy.

1.3   Operative techniques in cardiac transplantation

1.3.1   Standard technique

Lower, Dong and Shumway described the classical technique of heart transplantation that retains the right and left atria of both recipient and donor[47]. Recipient cardiectomy is made by incision in the right and left atrium along the atrioventricular groove. The aorta and pulmonary trunk are transected above the semilunar commissures and separated. Pulmonary vein orifices of donor heart are connected with a left atrial incision. The left atrium of the donor is anastomosed to that of the recipient. After left atrial anastomosis, a right atrial incision is made from the inferior vena cava toward the vena cava superior. The right atrium (RA) of the donor is anastomosed to the right atrium of the recipient, and the pulmonary trunk and aorta are anastomosed end to end.

1.3.1.1 Modifications of standard technique

The original Lower-Shumway technique was the first technique for heart transplantation in which insertion was performed from the inferior vena cava to the superior vena cava (Figure 1). This technique was later modified by Barnard and Cooley to prevent complications in the conduction system of the heart[1, 48] (Figure 2). In this modified technique, insertion was performed from the IVC to the right appendage of the heart. Years later, in 2006, Fraud *et al.* described a new technique designed to preserve the right heart geometry. With this technique, the donor atrium is opened along the posterior wall. The sinus node and right atrial appendage are preserved. The donor right atrium is anastomosed to the recipient's cavo-atrial cuff. In effect, this technique is nothing more than the original anastomosis technique of Lower and Shumway[49]. Another modification of the standard technique is the generous use of right atrial cuff with standard transplantation technique to reduce the tension between the anastomoses in order to preserve right atrial geometry[37].
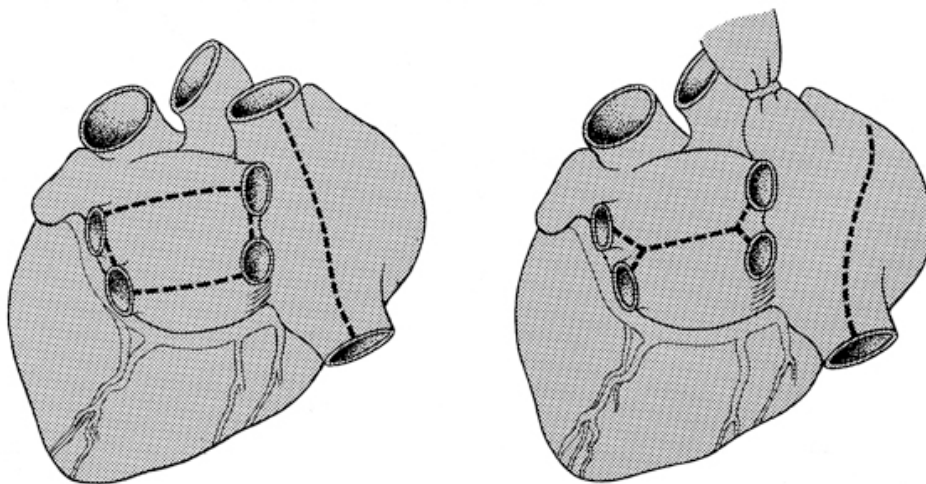
Figure 1 Preparation of left and right atrium in original Lower Shumway technique –left and Cooley and Barnard modified technique -right. In Cooley and Barnard modified technique the right atrium is opened from the lateral IVC toward the right atrial appendage to preserve conduction system.
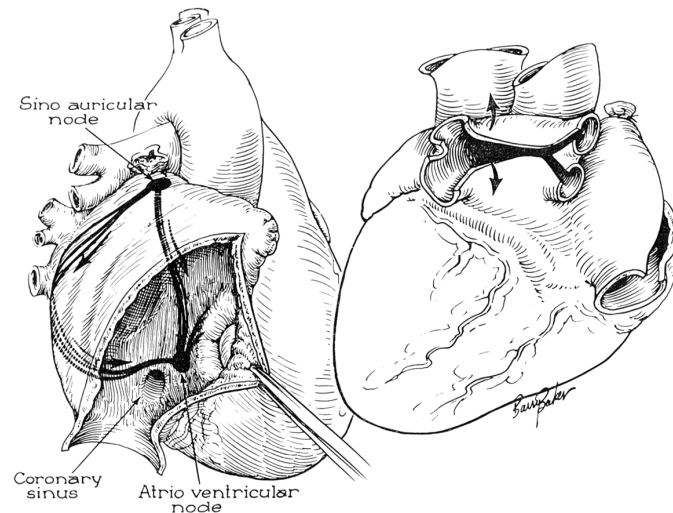
Figure 2 Preservation of the conductance system in the by Cooley and Barnard modified Lower-Shumway technique (Cooley *et.al.*; Cardiac transplantation: general considerations and results.)[48].

1.3.2 Bicaval technique

With the bicaval technique the right atrium is completely excised[50]. The vena cava superior and vena cava inferior are divided, leaving generous cuff of the inferior vena cava. Left atrial anastomosis is performed as in the standard technique. IVC and superior vena cava are anastomosed end to end. SVC length must be appropriate to avoid traction or kinking. Transplantation is completed with end-to-end anastomosis of the pulmonary trunk and aorta.

1.3.2.1 Modifications of bicaval technique

Marelli *et al.* favoured the use of a modified bicaval technique. The technique consists of the attachment of a triangular flap of the recipient's right atrium tissue to the anterior aspect of the native IVC remnant in order to reduce stress caused to the right atrium of the donor heart by the standard bicaval technique, which can produce tension on the tricuspid valve annulus and lead to insufficiency[51] (Figures 3, 4).

A   B
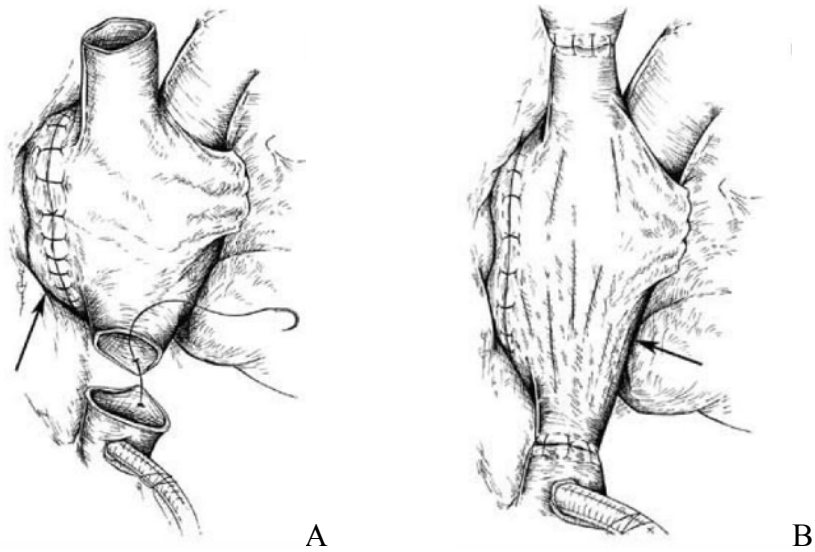
Figure 3 Tension on right atrium in the bicaval anastomosis. A) The anastomosis of left atrium affixes the posterior side of the right atrial septum. B) Tension on the tricuspid valve annulus due to right atrium distortion resulted with increased distances in the recipient pericardium. (Marelli *et al.*; Modified inferior vena caval anastomosis to reduce tricuspid valve regurgitation after heart transplantation 2007[51])
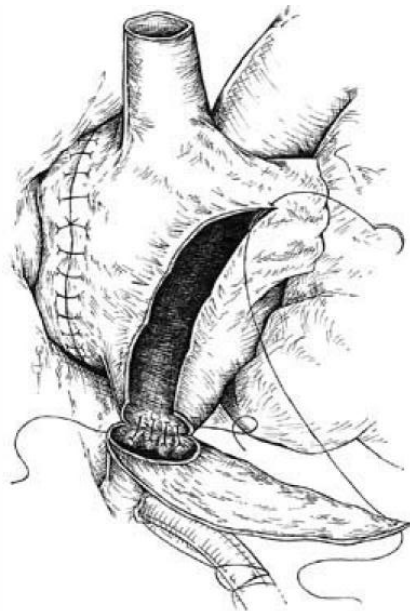
Figure 4 Modified inferior vena cava anastomosis using flap of the recipient's right atrium. (Marelli *et al.*; Modified inferior vena caval anastomosis to reduce tricuspid valve regurgitation after heart transplantation 2007)[51]

1.3.3   Total orthotopic technique

Sarsam *et al.* introduced an alternative technique, known as the total orthotopic technique, that preserves the shape of the left atrium and leaves the right atrium intact[52]. In this technique, the recipient atria are completely excised leaving the SVC, IVC and pulmonary venae. Transplantation is made through bicaval and pulmonary venous anastomoses.

1.4   Anatomy and function of the tricuspid valve

The tricuspid valve lies between the right atrium and right ventricle. It is composed of anterior, posterior and septal leaflets attached via chordae tendineae to papillary muscles and a fibrous annulus. The coronary sinus, atrioventricular node, and right coronary artery are surrounding structures of surgical importance[53]. The tricuspid valve leaflets are unequal in size: the anterior leaflet is the largest of the three and extends anteriorly from the infundibula region to the posterior inferolateral wall; the septal leaflet extends from the interventricular septum to the posterior ventricular border and the posterior leaflet from the septum to the inferolateral wall. The septal insertion of the tricuspid valve is also apical[54].

In the tricuspid insertion, the tricuspid annulus provides strong support. There are two high points and two low points in the tricuspid annulus, which is a non-planar in structure with an elliptical saddle-shaped pattern. In adults, the normal diameter of the tricuspid valve annulus is 28+5 mm in echocardiographic four-chamber visualization. A systolic tricuspid annulus diameter of 3.2 cm and diastolic tricuspid annulus diameter of 3.4 cm are widely used as important markers to identify the severity of TI[55]. The contraction of the tricuspid annulus and its normal motion are also helpful to maintain valve competence. The normal annular contraction of the tricuspid valve in systole is about 25%. Such information is highly valuable for tricuspid valve repair during surgery[56]. The tricuspid valve is usually supported by three papillary muscle groups, namely anterior, posterior and septal. Each of these papillary muscles is of a different size: the septal and anterior are larger than the posterior papillary muscles. One of the largest papillary muscles, the anterior muscle, is found to be linked with

moderate bands[54]. Under each leaflet, chordal attachments are connected to one or more papillary muscles[57].

1.5   Tricuspid insufficiency

TI is a disorder where the tricuspid valve of heart does not close properly, which causes blood to leak into the right atrium when the right ventricle contracts. It is mostly asymptomatic. Patients with severe TI have symptoms of fatigue and weakness. It can lead to peripheral edema, ascites, congestive hepatosplenomegaly, pulsatile liver and pleural effusions consequent to reduced cardiac output[53].

1.5.1   Etiology

Mild degrees of TI commonly occur in the non-transplantation population with an incidence of 65-75 percent[58]. A proper understanding of leaflet morphology is important to develop and use advanced techniques of valve repair and to design a suitable annular ring for surgical therapy of TI. TI is usually identified in patients with multiple valvular disorders, specifically mitral or aortic valve disease[54].

Impaired valve coaptation is the main cause of TI, which is caused by dilation of the tricuspid annulus and right ventricle. Valve incompetence can be caused by a number of primary disease processes such as infective endocarditis, congenital disease like atrioventricular canal, carcinoid syndrome, rheumatic fever, endomyocardial fibrosis, prolapse due to myxomatous degeneration of the tricuspid value, iatrogenic damage during cardiac surgery, catheter placement in the right heart chamber, penetrating and non-penetrating trauma and biopsies[54]. Functional TI is caused by changes in right ventricle morphology and annular dilatation that can result from left sided heart disease, cardiomyopathy, congenital heart defects, pulmonary hypertension or end-stage renal disease[59,60].

1.5.2 Diagnosis

The systolic murmur of TI is holosystolic. The murmur of TI starts with the first heart sound. The duration of the murmur and loudness may differ depending on the regurgitation magnitude. The murmur is heard to the left of the sternum's lower end and is accentuated during inspiration because of physiologic venous return. TI may result from alteration of the structure of any one or all of the components of the apparatus of the tricuspid valve. Components include the chordae tendineae, leaflets, adjacent right ventricular muscles, the papillary muscles and valve annulus.

The hemodynamic alterations are based on the duration as well as gravity of TI and incorporate a high right atrial average strain including a systolic v wave in addition to decreased cardiac output[61]. Hemodynamic catheterization is hardly ever necessary to validate the finding of TI, and right ventriculography is appropriate as the catheter might provoke TI. To validate the existence, gravity and etiology of TI and its influence on right ventricular dimension and performance, 2-D echocardiography offers good morphological evaluation of the tricuspid valve and right ventricle[56, 62].

TI can be qualitatively as well as semi-quantitatively ranked by means of Doppler imaging. About 80 to 90 percent of patients asked to undergo echocardiography possess a certain level of TI[63]. A thick "dagger-shaped" early-peaking systolic continuous-wave Doppler indication is acceptable with acute TI owing to untimely equilibration of right atrial and right ventricular strains. The vena contracta, established using color-flow Doppler, in a roundabout manner mirrors the effectual regurgitant orifice region (acute TI exists when >0.7 cm) [64, 65]. Quantitative evaluation is further possible by means of the proximal isovelocity surface region technique. Different secondary results of acute TI comprise lesser vena cava dilatation as well as systolic hepatic vein flow setbacks that might not be certain for acute TI if atrial fibrillation exists[64, 66].

1.6 TI after HTx

1.6.1 Etiology

Many hypotheses have been proposed for the causes of TI after transplantation. The causes can be divided into anatomical and functional or early and late. Anatomic TI after HTx can be caused by endomyocardial biopsy, trauma, catheter placement or infective endocarditis, whereas functional TI can be caused by the surgical technique, preoperatively high pulmonary artery pressure, allograft rejection, mismatch of donor heart and pericardial cavity or right ventricular dysfunction.

The existence of pulmonary hypertension and right ventricular injury can possibly cause right ventricular and tricuspid dilatation, which can subsequently cause TI. With regard to non-transplant patients, the pressure of the pulmonary artery ranges above 55 mmHg which is correlated with functional TI[10]. A study by Hausen *et al.* suggested that patients with postoperative vascular resistance greater than 240 dynes s/cm5 are highly prone to early postoperative TI[2]. Another research study revealed that pulmonary hypertension before transplantation and increased pulmonary vascular resistance after transplantation were correlated with significant TI[67]. Williams *et al.* conducted a study with 72 orthotopic cardiac transplant patients and reported that early postoperative pulmonary hypertension resolved in most post-transplant patients[6]. Statistical data from other studies such as Rees *et al.* indicates no effective association between preoperative systolic pulmonary arterial pressure (SPAP), postoperative pulmonary vascular resistance (PVR) and postoperative TI. Their research study was conducted on patients only for 5 months post-transplant, only 6 patients had balanced TI and none suffered from serious TI [68]. Similar results were obtained by Lo *et al.* who reported that no significant dissimilarities were found between postoperative PVR and SPAP and different severities of TI[69]. Another two studies have determined that there is no correlation between the *pre*-transplant pulmonary artery pressure, pulmonary vascular resistance and subsequent development of severe TI[2, 70].

The study by Aziz et al. found that allograft rejection beyond Grade 2 independently predicts early TI after HTx[18].

In orthotopic heart transplantation, three main techniques are employed: the bi-atrial, bicaval and total orthotopic techniques. The first, the bi-atrial technique, links recipient and donor atrial cuffs. The second, the bicaval technique connects the superior and inferior vena cava of the donor and recipient heart through anastomoses. In the third, the total orthotopic technique, the recipient atria are completely excised through discrete bicaval end-to-end anastomoses in addition to pulmonary venous anastomoses. Morgan and Edward reviewed 39 studies on HTx and compared the consequences of these three techniques. They concluded that bicaval techniques provide functional advantages such as reduced valvular insufficiency over others[71]. Another study by Yankah et al. reported that use of the Lower and Shumway technique facilitated low TI incidence after orthotopic transplantation in 1,124 patients when a generous right atrial cuff was used[37]. Aziz et al. found a rise in the occurrence and progressive evolution of TI in patients who underwent the biatrial technique vs. those who had a bicaval approach (41% at 1 month, 52% at 24 months vs. 15% at 1 month, 30% at 24 months, respectively)[18].

Haverich et al. proposed that TI is due to the mismatch in the size of the heart of the donor and the pericardial cavity of the recipient, which results in distortion surrounding the tricuspid valve ring[72]. The large right atrium with abnormal geometry of the tricuspid annulus created due to surgical atrial anastomosis can also lead to TI[70, 73].

The importance of atrial geometry was shown in a study by De Simone et al. in which the role of recipient/donor (R/D) right atrium ratio was investigated[15]. Dandel and his team showed that patients without TI had a D/R ratio of <1, whereas those with severe TI had D/R >1[74]. One study that focused on annulus diameter and overall atrial dimensions in MRI and echocardiography found overall right atrial diameter and native recipient right atrial diameter to be risk factor for TI after Htx. It showed once more that annulus dilatation has progressive character and that there is a correlation between recipient native right atrium and overall right atrial diameter and tricuspid valve diameter distension[3].

TI can be directly induced through anatomic interruption of the valve apparatus such as torn leaflet or ruptured chordae tendineae at the time of endomyocardial biopsy which is used to diagnose allograft rejection[17, 22].

In the early 1990s, EMB was identified as the main cause for post-transplantation TI. This has been evident since Braverman *et al.* conducted a study with 81 orthotopic heart transplanted patients[75]. Out of 81 patients, five were reported to have TV chordae rupture after transplantation. Several reports such as these by Tucker *et al.* and Hausen *et al.* indicated that iatrogenic damage of the tricuspid valve was provoked by EMB[2,76].

The risk factors of EMB may fluctuate depending on the patient's clinical condition, operator's experience, access sites and the type of bioptome used[77]. Wiklund and colleagues reported that six out of 96 heart transplanted patients had an unexpected appearance of enormous TI. All were directly associated with a preceding EMB, with chordal tissue that was found histologically in the biopsy samples[78].

A study by Williams *et al.* identified flail tricuspid valve (FTV) as the main cause of severe TI after heart transplantation[6, 67]. A significant correlation between TI development and number of biopsies was identified by Hausen *et al.*[2]. A similar result was noted by Lo *et al.* who reported that iatrogenic damage of the tricuspid apparatus was responsible for the occurrence of moderate to severe TI and TI progression [69]. Also they reported that the incidence of iatrogenic damage was directly correlated with the number of biopsies.

1.6.2 Risk factors

There are various factors that influence pathophysiological mechanisms which might lead to TI. Mostly during transplantation, the donor heart is investigated thoroughly and hence the incidence of an unrecognized primary valvular lesion is extremely low.

The causes behind TI soon after heart transplantantation beginning with the intraoperative phase, differ: the right atrium geometry modification is the effect of anastomosis of the right atrium when applying the cardiac orthotopic transplantation technique, the atrium twist that occurs during ventricular systole and ventricular diastole, the atrial contraction asynchronicity that happens in the donor and the recipient's atrial compartment, the dysfunction of papillary muscles[14, 15, 79]. Another risk factor is the post-transplant cardiac dilatation that can occur due to pulmonary hypertension and right ventricular dysfunction[17, 18, 80]. TI can also be also correlated with allograft rejection grade[189].Patients who have had more EMBs may also have had more allograft injury from

rejection[18]. One of the most commonly agreed risk factors for TI after orthotopic HTx is an EMB procedure complication which can disrupt the tricuspid valve appatatus[17].

In year 1990 it was found that tricuspid, mitral and pulmonary regurgitation was more common in patients who underwent heart-lung transplantation than in normal patients [81]. In the 1990s tricuspid insufficiency after cardiac transplantation gathered high interest and although many studies were conducted to identify the risk factors of TI development after HTx until now there is considerable ambiguity.

Williams *et al.* performed a study in 72 patients with moderate to severe TI. They noted that 23 patients had higher right atrial pressure, greater right-side cardiac dimensions and lower cardiac index [6].

Sade *et al.* found that the operating time was longer for patients with significant TI at follow-up. These patients were also significantly older at operation time compared to the group without significant TI. Their body surface area was greater, echocardiographic and radionuclide right ventricle ejection fraction was lower and exercise perfusion abnormalities and systolic blood pressure were greater. The surgical technique of bicaval or biatrial anastomosis did not have an influence on early TI development[82].

The number of endomyocardial biopsies is considered a significant risk factor. Sun *et al.* stressed that the mean number of endomyocardial biopsies during follow-up term was significantly greater in the group that had developed significant TI at the termination of follow-up[83].

Lewen *et al.* conducted a study with 20 patients who had undergone cardiac transplantation to identify Doppler detected TI. Age of patients, primary disease process, and severity of organ rejection, frequency of organ rejection and cold ischemic time of the transplanted organ showed no significant relationship with TI development. Two out of 20 patients had torn or partially torn tricuspid chordae and the remaining had functional TI. Before transplantation, eight patients had a pulmonary artery systolic pressure of 55 mmHg but after transplantation the patients were found to have significant TI. Similarly, patients did not show pulmonary vascular resistance before transplantation. However, after transplantation, pulmonary vascular resistance was increased significantly in patients with moderate to severe TI [67].

The significance of older donor age was observed in a new study by Kim *et al.* with excellent long-term results of tricuspid valve function after heart transplantation regardless of anastomotic technique[5].

A comparative study was conducted by Akasaka *et al.* to determine the prevalence of tricuspid, mitral and pulmonary regurgitation among normal and heart-lung transplanted patients. The study identified that factors such as age, donor organ total ischemic time, time after operation, steroid use for immune suppression, and number of rejection episodes had no significant effect on regurgitant jet area[84].

With 10 years of experience in HTx, the risk factors for TI were assessed by Aziz et al. A total of 249 patients were evaluated. This study showed that donor age, recipient age, ejection fraction, TPG, pre-operative PVR, pre-operative creatinine, pre-operative PAP, CI, pre-operative renal failure, duration of heart failure (HF), pre-operative NYHA III/IV, ischemic time, implantation time and cardiopulmonary bypass (CPB) time have no impact on TI after Htx. Results suggest that patients who underwent standardized operation technique showed greater incidence of TI than those with bicaval technique. A significant relationship was found between preoperatively raised transpulmonary gradient, rejection $\geq$ grade 2, increased pulmonary vascular resistance and early TI. In the case of late TI, factors such as total number of biopsies ($p < 0.02$), frequency of rejection $\geq$ grade 2 ($p < 0.004$) and standard techniques ($p < 0.0001$) were responsible for the development of late TI in transplanted patients.

In the study performed on 113 patients (56 with bicaval, 57 with biatrial technique) by Kalra *et al.,* no difference in early and late TI severity and velocity related to the anastomosis technique was found[85].

Park *et al.* compared the prevalent regurgitation of tricuspid after bicaval anastomosis and anastomosis with standard techniques. There were no differences in rejection treatment, immunosuppression, pre-transplant diagnosis, graft ischemic time or donor age between the two groups. The prevalence of TI was greater after the standard technique (36.4% vs. 10.5%; $p < 0.05$) was used[86].

Berger *et al.* studied the risk factors for tricuspid valve regurgitation after orthotopic heart transplantation. The study showed that the development of TI after HTx may be related

to the biatrial anastomosis technique and to graft vasculopathy. EMB, number of EMBs, PAP and pericardial cavity discordance showed no significance [87].

Sobczyk *et al.* performed a study to determine the incidence of subclinical and severe TI, to evaluate its clinical significance, and to assess the risk factors for TI in the heart transplantation population. The development of early TI was correlated with preoperatively raised transpulmonary gradients, raised vascular resistance and early rejection greater than or equal to grade 2 according to International Society of Heart and Lung Transplantation (ISHLT) criteria. Risk factors for late TI were: number of rejection episodes greater than or equal to grade 2 and the total number of heart biopsies. He concluded that prevalence may be lowered by early treatment of rejection and reduction of the number of biopsies performed[88].

Another study was conducted by Sivarajan *et al.* to determine the prevalence and risk factors for TI after pediatric heart transplantation. Development of significant TI was highly associated with graft failure. [89].

Nguyen *et al.* conducted study to determine a correlation between the severity of TI and the number of EMBs. The samples of 101 patients with HTx were taken between May 1987 and August 2001 and the number of EMBs performed in each patient was determined. Data on technique of anastomosis, liver and renal function, ejection fraction, and pulmonary artery pressure were also extracted. Echocardiography reports were reviewed to determine the presence and severity of TI. Multivariable analysis identified EMB as the only independent predictor of the severity of TI and there is a direct correlation between the number of EMBs and the severity of TI[90].

Mielniczuk *et al.* performed a study to determine whether the endomyocardial biopsy specimens of patients who developed significant tricuspid valve regurgitation (TVR) after cardiac transplantation had evidence of chordal tissue. Patients whose biopsy specimens evidenced chordal tissue tended to have a greater degree of TVR, but this was not statistically significant (odds ratio, 2.07; 95% confidence interval, 0.537-8.01, p = 0.32). There was no statistically significant difference in the number of biopsy specimens (p = 0.798), the number of rejection episodes (p = 0.73), or overall left or right ventricular systolic function between the patients with and without biopsy specimen evidence of chordal tissue disruption. This

study provided histologic evidence that chordal tissue damage can occur after cardiac biopsy, resulting in significant TVR; however, it was clinically well tolerated by affected patients[91].

A similar study was conducted by Lo *et al.* to determine the prevalence of EMB-related iatrogenic damage of the tricuspid apparatus following orthotopic heart transplantation and to evaluate its impact on the patients. The iatrogenic damage of tricuspid apparatus and serial change of TI were accessed with 2-D and Doppler echocardiography. It was concluded that the prevalence of iatrogenic tricuspid apparatus damage was high in this study. It contributed to the progression of TI significantly regardless of the damage severity[69].

Haverich et al. identified pre-, intra- and postoperative risk factors of TI. They concluded that size mismatch of donor heart and recipient pericardial cavity resulting in distortion of the tricuspid valve ring was a risk factor for TI after HTx[72].

De Simone and his team found an essential link between TI and the recipient/donor (R/D) right atrium ratio and the dimensions of the recipient atrium per se among those patients who underwent a biatrial cardiac transplantation. Dandel *et al.* (2001) found that patients without TI (67%) had a D/R ratio of <1, when compared to those with severe TI with a D/R ratio of >1[15].

1.6.3 Epidemiology

TI after orthotopic heart transplantation is a disease with significant prevalence. Several studies reported a high incidence of TI after orthotopic cardiac transplantation, ranging from 19 to 84 percent[17]. One research study indicated more moderate/severe TI in heart transplant patients than in normal subjects (12% vs 3%, $p = 0.05$)[6]The study by Lo et al. reported that 33 out of 39 patients were identified as having TI. Of these, 23 (59.0%) had mild TI, 8 (20.5%) had moderate and 2 (5.1%) had severe TI [69]. At the end of follow-up it was noted that 36 out of 39 patients had TI and prevalence rate was also modified, that is, 12 had mild TI (30.8%), 16 had moderate TI (41.0%) and 8 had severe TI (20.5%) [88].

Williams *et al.* noted a 32 % occurrence of moderate or severe TI [6]. Hausen *et al.* recorded "grade 3" echocardiographic, moderate/severe TI developing in 50% of the respondents by 4 years after the transplant[2]. TI of any grade was observed in all the patients

after HTx in a study performed by Sobczyk on 326 patients. In this study TI greater than or equal to grade 2 was determined in 285 patients (87.96%). Early occurrence of TI was observed in 80 (28.07%). The incidence of TI after Htx in the study conducted by Nguyen *et al.* showed that 25 (25%) of 101 patients had evidence of severe TI, whereas 76 (75%) had non-severe TI[90]. Another study by Berger *et al.* revealed 14.1% TI prevalence after transplantation[87]. Yankah *et al.* demonstrated 5.5% prevalence at the end of follow-up [37]. Rees *et al.* noted that 12% of patients had restrained TI and none had acute TI[68]. Lewen *et al.* noted that 20% had acute TI and 50% restrained TI, but this research included only 20 respondents [67]. Chan *et al.* carried out the most extensive research, including 336 respondents. Ninety (27%) patients had moderate TI and 23 (7%) patients had severe TI [92]. Marelli *et al.* conducted a study with 670 patients and identified 78% with freedom from significant TI at 9 years[93]. A similar study conducted by Berger *et al.* identified 85.2% at 10 years[87].

1.7 Statement of the problem

The occurrence of TI is common after orthotopic heart transplantation and the prevalence ranges from 19% to 84%[17]. Length of follow-up has an influence on severity of TI and although it is normally asymptomatic, sometimes it can be serious and lead to mortality[93]. Its severity can be appropriately measured using Doppler echocardiography[64, 94]. Use of diuretics is the common treatment method for severe TI. Tricuspid valve repair or replacement surgery may be required in refractory cases. TI after HTx etiology are ambiguous and require multifactorial analyzes of preoperative, intraoperative and postoperative causative factors.

A number of factors are found to be connected, including surgical anastomosis technique, multiple acute cellular rejection episodes (ACR), iatrogenic damage because of endomyocardial biopsies, pretransplant pulmonary hypertension, dissimilarities between the recipient's pericardial cavity and donor's heart size, ischemic injury of papillary muscles during transplantation, systolic pulmonary artery pressure elevation, cardiac allograft vasculopathy, and elevated pulmonary vascular resistance [2, 18, 69, 72, 90, 91, 93].

Although previous studies have shown different risk factors, there is a paucity. There is no study which analyses all of following risk factors which possibly can influence both anatomic and functional TI after HTx such as the age, sex, height, body mass index of the recipient, body surface area of recipients, donor to recipient right atrium anterior wall ratio, heart-lung ratio on X-ray, number of biopsies, number and degree of acute rejections, degree of CAV and dialysis. In addition, previous studies also showed inconsistency in reporting the risk factors. Previous studies have already highlighted that even mild intraoperative TI ($\geq$ grade 2) development after organic heart disease (OHD) leads to morbidity and death. Thus, it is imperative to determine the risk factors of TI after OHD. Against this background, the present study has attempted to examine possible risk factors for TI.

1.8   Aim of the study

The aim of the present study is to identify the risk factors that predict TI after heart transplantation

Specific objectives of the study are as follows:

1. To assess the incidence of tricuspid valve regurgitation after heart transplantation at Deutsches Herzzentrum Berlin
2. To identify the risk factors of TI
3. To correlate severity of TI after HTx with risk factors
4. To identify mechanisms of occurrence of TI after a heart transplantation
5. To suggest strategies for TI prevention after a heart transplantation.

2   Materials and methods

2.1   Type of study

The study is a retrospective single-institution cohort study.

2.2   Study population

Between 1986 and 2010 at Deutsches Herzzentrum Berlin, 1515 patients underwent HTx for the first time. We identified TI in 857 patients who survived at least 12 months and had echocardiographic assessments.

In a study population of 152 patients who underwent HTx between 1986 and 2000, using standard operation technique with generous use of the right atrial cuff, survived at least 12 months, and had all necessary variables known from the literature that can potentially influence anatomic or functional TI after cardiac transplantation. These variables were analyzed.

The group of 152 patients defined as representative was divided into two subgroups based on the severity of their postoperative TI: no TI to moderate (TI ≤2) and severe (TI >2). These two groups were compared regarding underlying disease, gender, age, height, weight, BMI, BSA of donor and recipients, organ ischemic time, preoperative pulmonary pressure, donor to recipient right atrium front wall ratio, tricuspid anterior to septal annulus systolic excursion ratio, ratio of thorax length to heart length on X-ray preoperatively, number of biopsies, the highest rejection grade in biopsy, the number of biopsies with more than moderate reaction, evidence of transplant vasculopathy on biopsy or need for chronic dialysis.

2.3 Exclusion criteria

Patients with torn or perforated leaflet and ruptured chordae of the tricuspid valve acquired iatrogenically at the time of biopsy were excluded from this study.

2.4 Outcome variables

The variables known from the literature that can affect TI such as underlying disease, gender, age, height, weight, BMI, BSA of recipients and organ ischemic time are collected from the patients' data.

Pulmonary pressure (mean, systolic and diastolic) was measured preoperatively with catheter during routine angiography; this procedure was not applicable in patients with a ventricular assist device. The right atrium front wall ratio and tricuspid anterior to septal systolic annulus excursion ratios was estimated for both donors and recipients in the year 2001 during TI evaluation on echocardiography. The ratio of thorax length to heart length on X-ray was measured from preoperative X-rays. Necessity of chronic dialysis was also noted during the last 2 years of the study period.

Orthotopic implantation of the donor heart was carried out using the Lower and Shumway technique as modified by Cooley and Barnard [95].For anastomosis without tension on and preservation of right atrial geometry, a generous atrial cuff was used.

2.5 Evaluation

2.5.1 Non-invasive evaluation

TI was quantified by Doppler color flow imaging using the proximal convergence method, colour jet mapping and vena contracta imaging. The maximal area of the color Doppler regurgitant jet to the atrial area and pulsed-wave evidence of systolic reversal of flow in the hepatic veins showing trace $\ll 10\%$, mild 10–24%, moderate 25–50%, severe

≫50% were used to assess the TI[68, 96]. The ratio of the regurgitant jet area to the atrial areas manifests the severity of TI.

Donor to recipient right atrium and anterior wall ratio was evaluated during transthoracic echocardiography in the modified apical four-chamber view, where the right atrium anterior wall can be viewed and lengths can be measured (Figure 5).
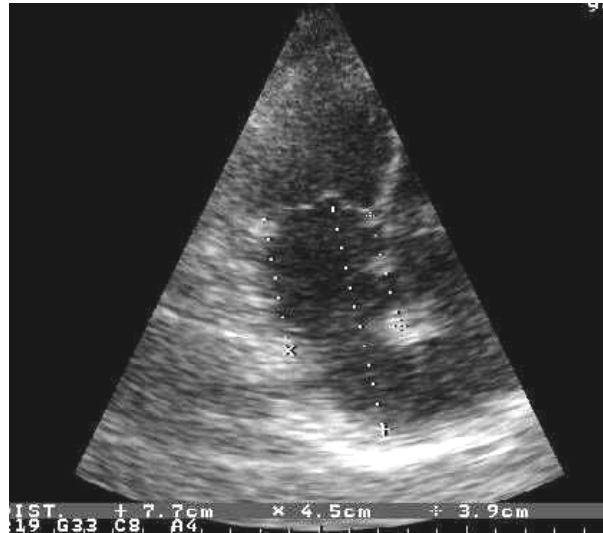
Figure 5 Modified apical four-chamber view to visualize and measure the length of right atrium anterior wall of donor and recipient.

Tricuspid annulus anterior to septal systolic excursion ratio (Figure 6) was calculated from data acquired in the four-chamber view measuring the amount of longitudinal motion of the annulus in the anterior and septal part at peak systole.

Thorax and heart width was measured on preoperative X-ray pictures. Cardiac length was measured between the maximum transverse cardiac diameter and the maximal thoracic diameter as measured between the inner margins of the ribs.

Figure 6 Tricuspid annulus anterior to septal leaflet systolic excursion ratio measurement in the apical four chamber viewof transplanted heart.

2.5.2 Invasive evaluation

All patients underwent classic triple immunosuppressive therapy with cyclosporine, azathioprine or mycophenolate mofetil and steroids. Surveillance echocardiography and right heart catheterization was performed annually. The maximal amplitude of QRS-complex rejection was monitored every day by using telemetric intramyocardial electrocardiography. Only for doubtful IMEG echocardiographic findings were endomyocardial biopsies with a 45-cm sheath bioptome and right internal jugular approach performed. Biopsies were evaluated for rejection using the revised ISHLT criteria.

Evaluation of transplant vasculopathy was done by annual coronary arteriogram. In the presence of ≥75% luminal stenosis in coronary angiography light microscopic evaluations were performed for microvasculopathy.

Degree of allograft microvasculopathy was graded using the following classification used by the Deutsches Herzzentrum cardiovascular pathology group:

1. 0/0 Endothelial cells inconspicuous, no vessel wall thickening, no proliferation
2. 0/1 Endothelial cells inconspicuous, mild vessel wall thickening by proliferation
3. 0/2 Endothelial cells inconspicuous, intensive vessel wall thickening by proliferation
4. 1/0 Endothelial cells prominent (not swollen), vessel wall inconspicuous
5. 2/0 Intensive endothelial cell swelling, vessel wall inconspicuous
6. 2/1 Intensive endothelial cell swelling, mild vessel wall thickening by proliferation
7. 1/1 Mild endothelial cell swelling, mild vessel wall thickening by proliferation
8. 1/2 Mild endothelial cell swelling, intensive vessel wall thickening by proliferation
9. 2/2 Intensive endothelial cell swelling, intensive vessel wall thickening by proliferation

2.6   Statistical analysis

The statistical analyses were performed using SPSS 22.0 version (SPSS Inc., USA). The metric variables were represented as mean and median values, while the scattering measurements were expressed as standard deviations and quartiles.

The scale variables were checked by the Kolmogorov-Smirnov test ($p \geq 0.05$) in relation to their normal distribution. Since some of the variables were not distributed normally, non-parametric test was used for non-normally distributed samples.

The T-test was used to compare two independent, normally distributed random samples. Previously, the Levene test was applied to verify the homogeneity of the variances. For non-normally distributed random samples, the Mann-Whitney U-test was used as a non-parametric method.

The categorical data were evaluated using the chi-square test or the Fisher exact test.

In all the tests performed, there was a two-sided significance testing, wherein a p-value <0.05 was taken as statistically significant for all statistical tests.

The survival statistics were performed using Kaplan-Meier analysis, and log rank analysis was used to compare mortality rates. For multivariable analysis, binary logistic

regression with Wald-Statistics and inclusion-forward using the likelihood ratio criterion (including p-value ≤ 0.05; p-value exclusion > 0.1) was performed.

Graphs were created using SPSS, with error bars used to illustrate the mean values for normally distributed samples. Similarly, the degree of scatter due to the large scattering width of the standard errors was also listed. For the non-parametric test, medians and interquartile distances were used in the graph using sample box plots. While in the boxes, the median and the 25th-75th percentiles are plotted, the T-bars corresponding to the minimum and maximum values were marked unless they are outliers or extreme values. Outliers are values between 1 ½ - 3 box lengths outside the box and are shown in the graphs as circles, while extreme values that were measured more than 3 box lengths outside the box are plotted as crosses. The categorical data were graphically represented using clustered bar charts.

2.7   Ethics

The procedures followed were in accordance with the ethical standards of the Institutional Human Ethics Committee and with the Helsinki Declaration. This study was approved by our Institutional Review Board, with the need for patient consent being waived.

3 Results

3.1 Study group

Between 1986 and 2010 1515 adult patients underwent heart transplantation at the the Deutsches Herzzentrum Berlin (DHZB). 857 out of 1515 adult patients survived at least 12 months and had information concerning TI in echocardiographic assessments, 38% (n=327) had no TI, 43 % (n=369) TI I, 13% n= (109) TI 2, 5% (n=42) TI 3 and 1% (n=10) TI 4. (Figure 7)

In the study group of 152 patients who underwent HTx between 1986 and 2000 at the same institution, survived at least 12 months and had available the necessary variables known from the literature that can potentially influence anatomic or functional TI after cardiac transplantation, echocardiographic assessment showed 37% (n=56) TI 0, 43% (n=65) TI I, 12% (n= 19) TI 2, 6% (n= 9) TI 3 and 2% (n = 3) TI 4. The distribution of TI in this group allows us to classify this group as representative of the group of 857 patients. (Figure 8) The representative group was divided into two groups based on the severity of postoperative TI (TI ≤ 2 92.1% n=140 and TI >2 7.9% n=12) and all variables were statistically compared in both groups.

The mean follow-up time was 9 years in the whole study group and 6 years in the representative group.
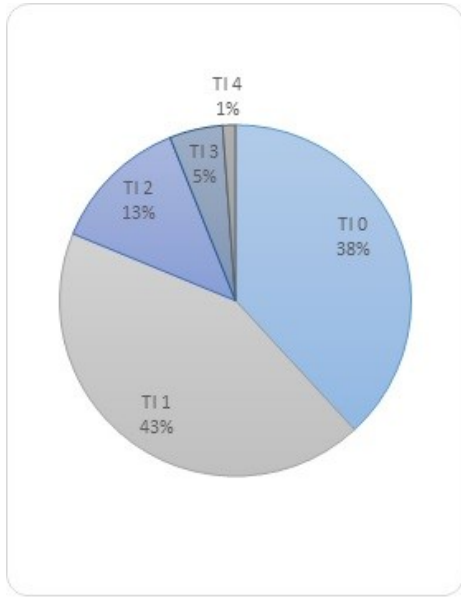
Figure 7 Incidence of TI after HTx in DHZB between 1986 and 2010 (n=857),TI 0 38% (n=327), TI 43 % (n=369), TI 2 13% n= (109), TI 3 5% (n=42), TI 4 1% (n=10)
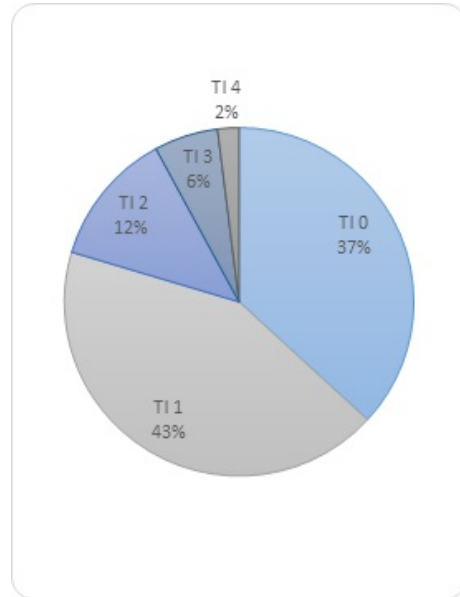
Figure 8 Incidence of TI after Htx in study group of 152 patients TI 0 37% (n=56) ,TI I 43% (n=65),TI 2 12% (n= 19) ,TI 3 6% (n= 9) and TI 4 2% (n = 3)

Table 1 Similarity of incidence of TI after HTx in entire patient group transplanted between 1986 and 2010 and in study group

	Between 1986 and 2010	**Study group**
TI 0	38% (n=327)	37% (n=56)
TI 1	43 % (n=369)	43% (n=65)
TI 2	13% n= (109)	12% (n= 19)
TI 3	5% (n=42)	6% (n= 9)
TI 4	1% (n=10)	2% (n = 3)

TI tricuspid insufficiency, n number,

3.2   Recipients' demographics and pre-operative events

The majority of the recipients were male: 85.5% (n = 130) and 14.5% (n= 22) female. In the male group, 92.3% had TI ≤2 and 7.7% TI >2. In the female group, 90.9 % had TI≤2 and 9.1% TI> 2. Since *p*=0.686, there was no significant difference between the two groups (Table 1).

When the underlying diseases were considered, it was found that 66.9% (n = 101) had dilative cardiomyopathy (DCP) and 27.2% (n= 41) coronary artery disease (CAD).

The age of recipient showed significant relevance (*p*=0.027) for the development of severe TI after HTx. Median age for the group with TI ≤2 was 52.06 years; the youngest patient was 22 and the oldest was 66 years old. For the group with TI>2 median age was 43.05, with the youngest patient being 26 and the oldest 60 years old. Recipients who developed TI>2 were younger than those with TI≤ 2 (Figure 9).
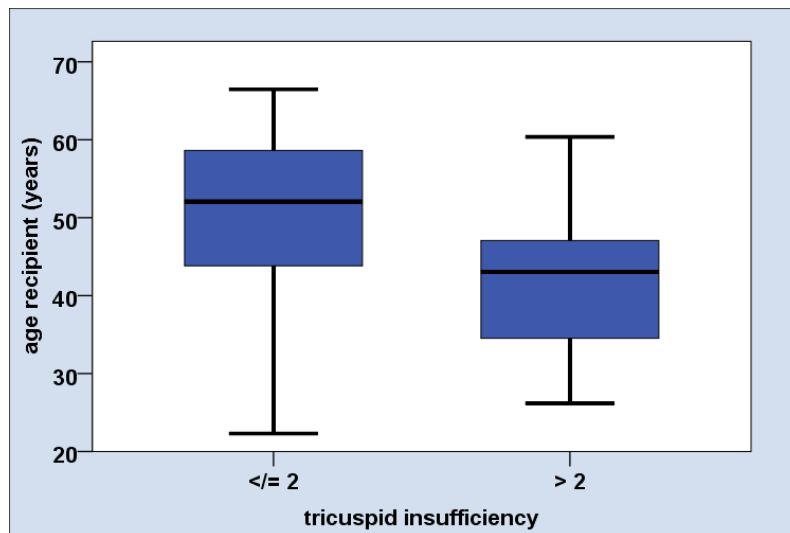
Figure 9 Comparison of recipients age in TI ≤2 vs. TI >2 group (*p* = 0.027)

Organ ischemia time showed no significance for severe TI after HTx.

There was no significance of height, weight, BMI, organ ischemia time or BSA of recipient, although height of recipient with p-value of 0.073 shows a trend towards significance. Median height of recipients with TI >2 was 176 cm whereas for recipients with TI ≤2 it was 174 cm (Figure 10).
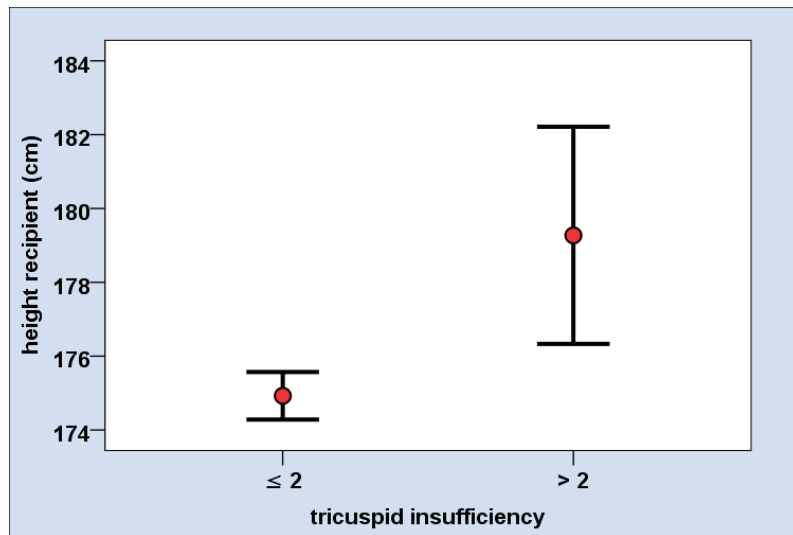
Figure 10 Comparison of recipients' height in TI ≤2 vs. TI >2 group (p = 0.073)

Table 2 Recipients' demographics and pre-operative conditions

	TI ≤ 2	TI > 2	*p*
Age (years)	49.55±11.2	42.4±10.39	0.027
Sex: female/male	120/20	10/2	0.686
Underlying disease CAD/DCM/other	40/91/8	1/10/1	0.309
Height (cm)	174±7.49	179.27±9.76	0.073
Weight (kg)	74.13±12.88	73.18±13.47	0.815
BMI (kg/m2)	24.44±4.61	22.96±3.03	0.271
BSA (m2)	1,89±0.18	1.90±0.22	0.831
PAP systolic (mmHg)	46.57±11.96	47±16.30	0.846
PAP diast. (mmHg)	24.17±7.46	24.22±8.53	0.803
PAP mean (mmHg)	32.19±8.73	31.27±12.13	0.709
Ischemic time (min)	163.85±48.41	163.75±46.50	0.995
	Mean ±SD	Mean ±SD	

TI tricuspid insufficiency, CAD Coronary artery disease, DCM dilative cardiomyopathy, BMI body mass index, BSA body surface area, PAP pulmonary artery pressure, SD standard deviation

3.3 Donor demographics

The majority of the donors were male with 70.2% (n= 106) and 29.8% (45) were female. Median age of donors was 35 years. The youngest was 13 years and the oldest 65 years old.

There were no notable differences in donor demographics such as age, sex, height, weight, BMI and BSA between the two groups and these variables showed no statistical significance for developing TI after cardiac transplantation.

Table 3 Donor demographics

	TI≤2	TI>2	*p*
Sex: male/female	97/42	9/3	0.496
Age (years)	35.29±13.87	35.25±13.19	0.910
Height (cm)	175.18±11.90	178±9.20	0.300
Weight (kg)	75.90±14.29	80.73±8.24	0.169
BMI (kg/m2)	24.42±4.13	25.21±2.71	0.405
BSA(m2)	1.92±.71	1.98±.14	0.277
	Mean±SD	Mean±SD	

TI tricuspid insufficiency, BMI body mass index, BSA body surface area, SD standard deviation

3.4 Functional TI

Geometric distortion, annular ring dilatation, mismatch of donor and recipient, pericardial cavity and malcoaptation of valve leaflets are the factors which can influence functional TI after HTx.

To detect geometry changes of right atrium as a risk factor that can influence functional TI after HTx, donor to recipient right atrial anterior wall ratio and tricuspid annulus anterior to septal leaflet excursion ratio we measured using echocardiography. We also analyzed the ratio of donor BMI to recipient, dimensions of recipient chest and heart on X-ray and necessity of dialysis.

Donor to recipient right atrial anterior wall ratio showed significance ($p<0.05$). The median for group with TI >2 was 1.25 and for group with TI ≤2 it was 0.85. (Figure 11)
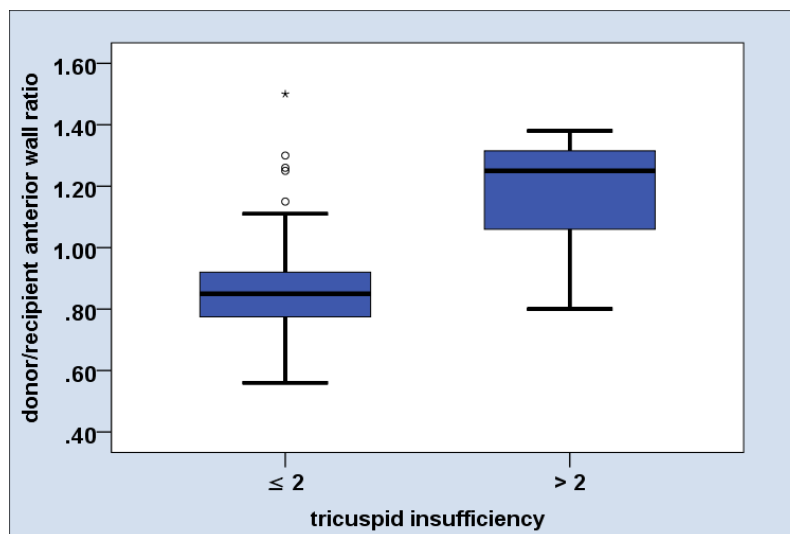
Figure 11 Comparison of donor to recipient right atrium anterior wall ratio in TI ≤2 vs. TI >2 group
($p<0.05$)

Tricuspid annulus anterior to septal leaflet excursion ratio was significant ($p<0.05$) for clinically significant TI after HTx. Due to the limits of transthoracic echocardiography, the

tricuspid annulus anterior to septal leaflet excursion ratio was known and valid in only 98 of 152, which made it impossible to use this parameter in multivariable analysis (Figure 12).
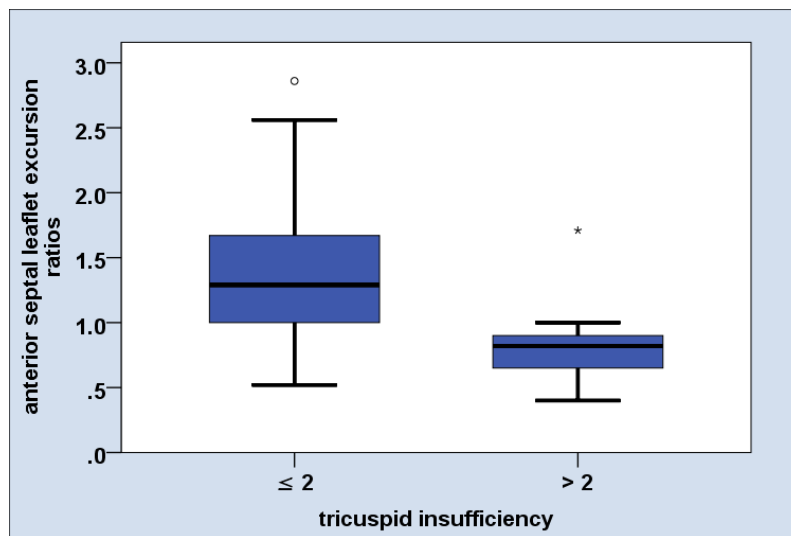
Figure 12 Comparison of tricuspid annulus anterior to septal leaflet ratio in TI ≤2 vs. TI >2 group (p<0.05)

BMI donor/ BMI recipient showed a small trend for significance with a p-value of 0.08 (Figure 13).
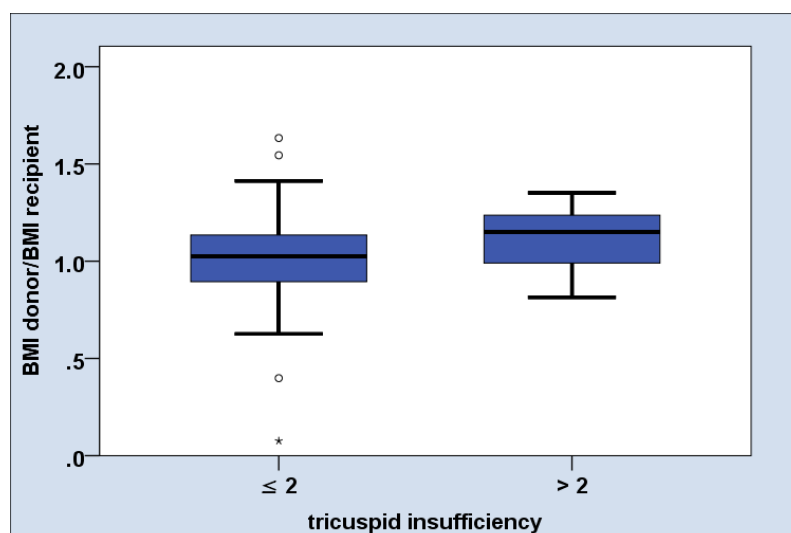
Figure 13 Comparison of donor to recipient BMI ratio in TI ≤2 vs. TI >2 group (*p*=0.080)

Dialysis is another pathologic factor that can play role in atrial size enlargement because of volume overload. Even though only 10 patients of 152 required dialysis, in 7 (5 %) responders from the group with TI ≤ 2 and 3 (27.3 %) from TI >2, dialysis shows significance (*p*=0.026) (Figure 14).
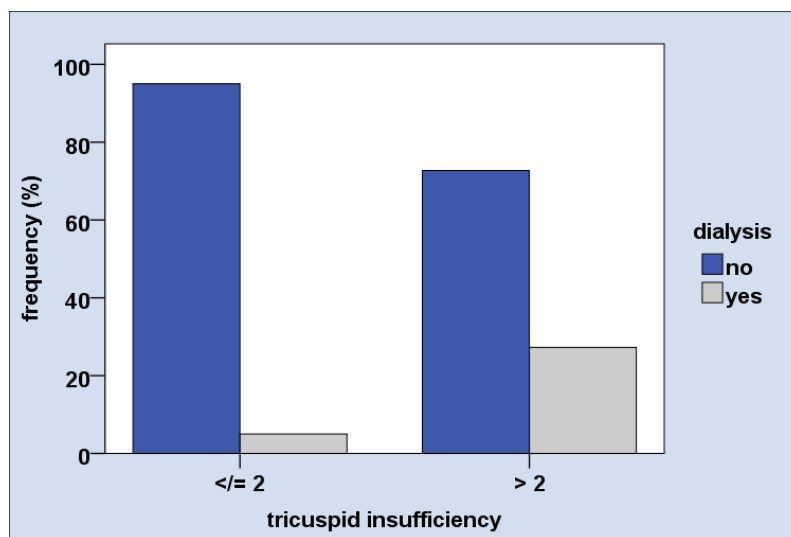
Figure 14 Comparison of dialysis in TI ≤2 vs. TI >2 group (*p*=0.026)

Thorax size, heart size on X-ray and their ratio showed no significance, but the size of heart and chest were bigger in the TI >2 group (mean =17,88; 30 cm resp.) than the TI ≤2 group (mean=16,43; 28,9 resp.) (Figure 15, Figure 16, Table 3).
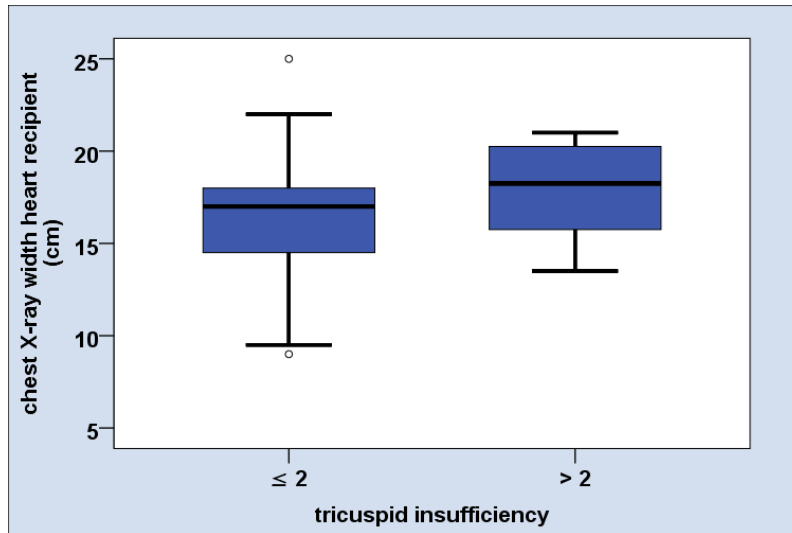
Figure 15 Comparison of recipient heart width on preoperative chest X-ray in TI ≤2 vs. TI >2 group
(*p*=0.131)
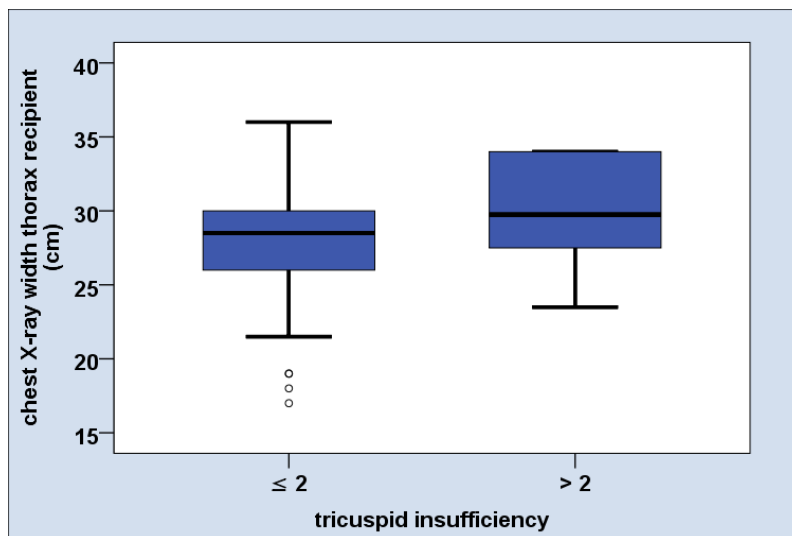
Figure 16 Comparison of Recipient thorax width on chest X-ray in TI ≤2 vs. TI >2 group (*p*=0.217)

Table 4 Parameters that can cause functional TI after cardiac transplantation

	TI≤2	TI>2	*p*
Donor recipient anterior wall ratio	0.85±0.14	1.17±.19	<0.001
Anterior septal leaflet excursion ratio	1.37±0.48	0.84±0.38	0.001
Chest X-ray width thorax recipient (cm)	28.09±3.58	30±3.85	0.217
Chest X-ray width heart recipient (cm)	16.43±2.72	17.88±2.75	0.131
X-Ray thorax heart ratio recipient	1.73±0.23	1.69±0.16	0.724
BMI donor to BMI recipient ratio	1.02±0.20	1.12±0.16	0.080
Dialysis yes(n) / no (n)	7/133	3/8	0.026
	Mean ±SD	Mean ±SD	

TI tricuspid insufficiency, BMI body mass index, SD standard deviation

3.5   EMB and cardiac allograft microvasculopathy.

TI caused by a known structural etiology such as torn or perforated leaflet and ruptured chordae at the time of EMB is the main exclusion criterion of the present study. We analysed variables such as total number of biopsies, highest diagnosed grade of biopsy, number of biopsies with more than moderate grade of rejection and degree of CAV in biopsy.

The total number of biopsies showed significance ($p=0.003$) with a mean value of 9.11 (SD ±2.72) and 26.92 (SD± 22.94) in the TI ≤2 and T >2 group, respectively (Figure 17).
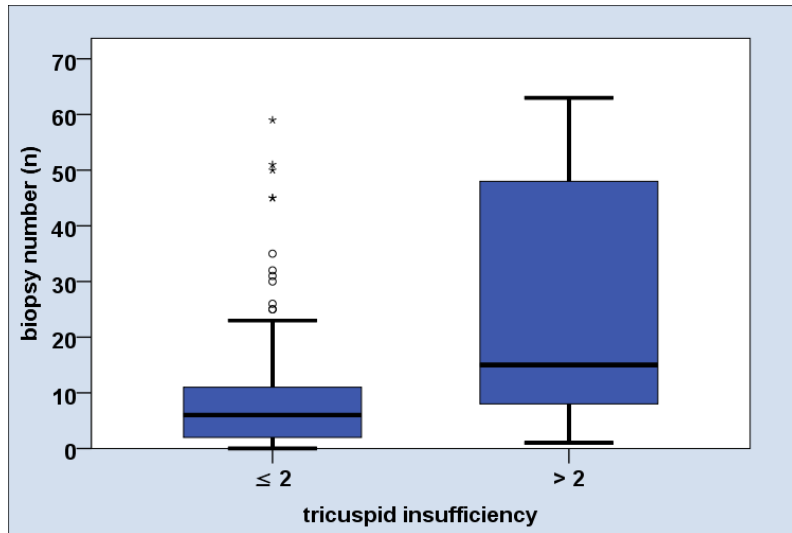
Figure 17 Comparison of total number of biopsies in TI ≤2 vs. TI >2 group (*p*=0.003)

A trend to significance (*p*=0.067) was found between TI >2 group and number of biopsies with a more than moderate grade. Patients with TI >2 had higher mean (mean± SD: 2.08±3.23) compared to patients with TI ≤2 (mean± SD: 0.56±1.14) (Figure 18).
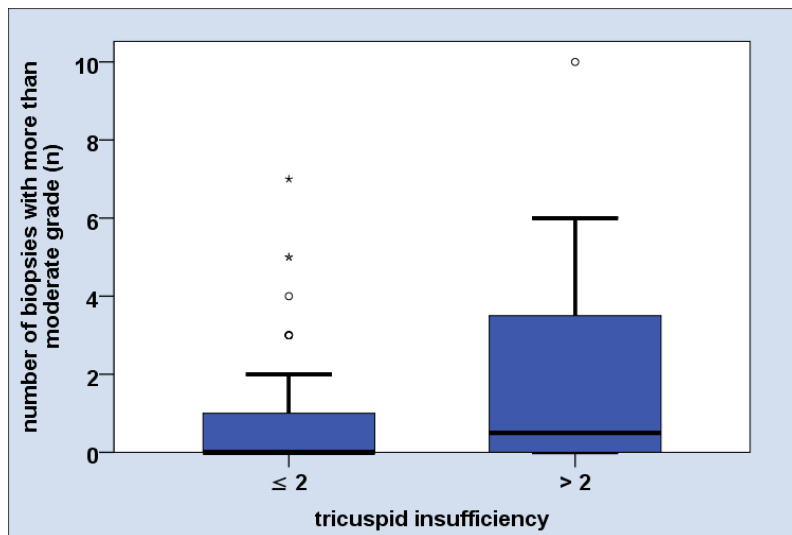
Figure 18 Comparison of number of biopsies with more than moderate rejection grade in TI ≤2 vs. TI >2 group (p=0.067)

Other parameters such as highest rejection grade showed no significance ($p>0.05$). The parameter showed a higher mean (mean± SD: 1.92±1.16) in the group with TI >2 than TI ≤2 (mean± SD: 1.36±1.19) (Figure 19, Table 5).
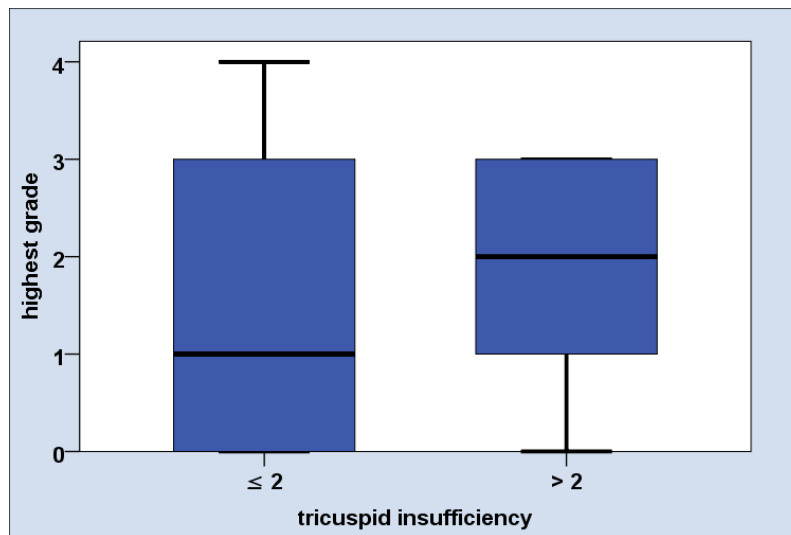
Figure 19 Comparison of highest rejection grade on EMB in TI ≤2 vs. TI >2 group (p=0.123)

Another variable which is known from the literature as a risk factor for developing TI is degree of CAV. We found that patients with TI >2 had a higher grade of allograft microvasculopathy than those with TI ≤2. However, it did not show significance (p=0.144) (Figure 20).
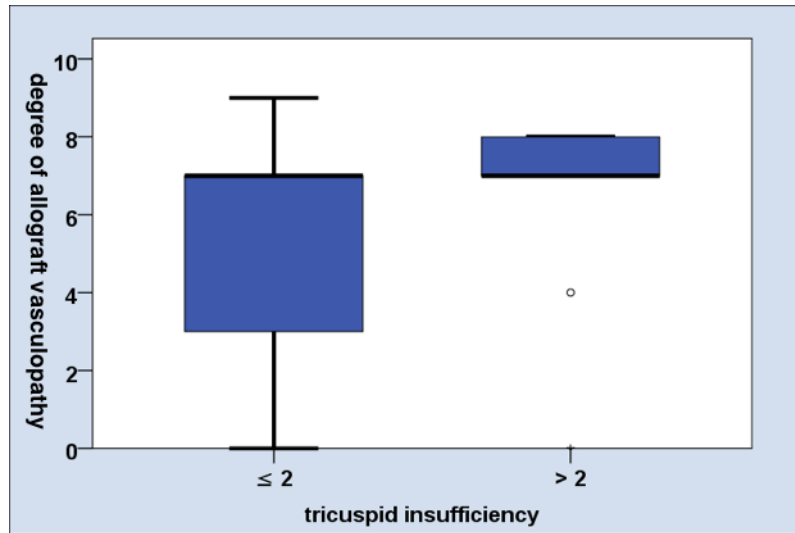
Figure 20 Comparison of degree of CAV grade in TI ≤2 vs. TI >2 group (*p*=0.144)

Table 5 Parameters that can cause anatomic TI after Htx

	TI≤2	TI>2	*p*
Total biopsy number	9.11±10.86	26.92±22.94	0.003
Highest biopsy grade	1.36±1.19	1.92±1.16	0.123
Number of biopsies with more than moderate grade	0.56±1.14	2.08±3.23	0.067
Transplant microvasculopathy	5.66±2.72	6.58±2.35	0.144
	Mean ±SD	Mean ±SD	

TI tricuspid insufficiency, SD standard deviation

3.6 Multivariable analysis

For multivariable analysis, binary logistic regression with Wald-statistics and forward inclusion using the likelihood ratio criterion (including p-value ≤ 0.05; p-value exclusion> 0.1) was performed. Parameters included for multivariable analysis are: age of recipient, donor/recipient anterior wall ratio basic disease, height of recipient, total biopsy number, degree of allograft microvasculopathy, and dialysis and BMI donor/BMI recipient. Because of the valid number of only 98, anterior/septal leaflet excursion ratio was not taken in regression. With p-value <0.05 in binary logistic regression, it is evident that the donor/recipient anterior wall ratio, biopsy number and dialysis have an independent association to TI.

Table 6 Variables with independent association to TI after Htx in logistic regression

	Wald	p
Donor/recipient anterior wall ratio	12.081	0.001
Total biopsy number	6.263	0.012
Dialysis	7.391	0.007

3.7 Survival

Kaplan-Meier analysis with log rank test value >0.05 shows no significance in mortality of patients with TI ≤2 and TI >2 (Figure 21).
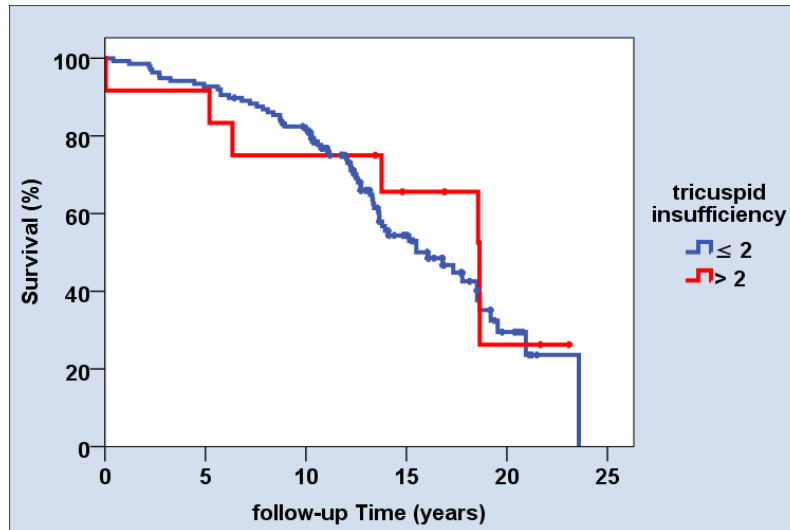
Figure 21 Kaplan-Meier survival graph in TI≤2 vs. TI>2 group

On actuarial analysis 99, 92, 66, 43 and 30 % of cardiac transplant survivors are expected to be alive with TI ≤2 at 1, 5, 13, 18 and 20 years with 135, 126, 59, 18 and 8 patients at risk respectively, compared with 92, 83, 75 and 26% of patients with TI >2 at 1, 5, 13 and 18 years with 11,10,8, 2 patients at risk respectively

Table 7 Comparison of survivors and patients at risk in TI≤2 vs. TI >2 group

	TI≤2		TI>2	
Time after Htx (year)	Survivors	Patients at risk	Survivors (%)	Patients at risk
1	99 %	135	92%	11
5	92%	126	83%	10
13	66%	59	75%	8
18	43%	18	26%	2

TI Tricuspid insufficiency, HTx Heart transplantation

Mean survival time was 15.6 (95% confidence interval (CI), 14,4 to 16,9) years for patients with TI ≤2 and 15.6 (95% CI 11.4 to 19.9) years for patients with TI >2.

Thus, there is an independent significant association between TI after HTx and donor/recipient anterior wall ratio, biopsy number and dialysis. Moderate to severe and severe TI have no significant effect on mortality after HTx.

4   Discussion

TI is common finding after cardiac transplantation. The cause of TI is multifactorial, and many hypotheses have been proposed. The major indications for heart transplantation are ischemic cardiomyopathy and dilated cardiomyopathy, but also valvular heart disease or congenital heart disease which has resulted in heart failure and is not accessible to surgical methods. The heart transplant patients were examined for presence of TI using echocardiography. The colour Doppler quantification method used here is the most widely accepted method[6, 68, 70]. The major causes of TI in the literature are the presence of pulmonary hypertension and right ventricular injury at the time of the transplantation, which leads to annular dilation of the right ventricle. Pulmonary artery pressure above 55 mm Hg is associated with functional TI in the normal population. Pulmonary hypertension before transplantation and elevated pulmonary vascular resistance after transplantation were associated with significant TI[67]. Surgical atrial anastomosis, which creates a large right atrium and abnormal geometry of the tricuspid annulus, might also lead to TI[15]. One study found no difference in the incidence and severity of TI at rest, but during exercise it found less TI in the bicaval group than in the standard atrial anastomosis group[73].

Several factors are responsible for development of TI, including multiple acute cellular rejection, iatrogenic damage due to EMB, surgical anastomosis technique, pretransplant pulmonary hypertension, size mismatch between donor and recipient, elevated systolic pulmonary artery pressure, pulmonary vascular resistance, ischemic injury of papillary muscular during transplantation and cardiac allograft vasculopathy [6, 15, 18, 37, 86, 97-101]. However, there is no consistency in previous studies reporting risk factors. Hence, a retrospective cohort study was conducted to:

1. assess the incidence of tricuspid valve regurgitation after heart transplantation at Deutsches Herzzentrum Berlin
2. identify incidence of TI
3. correlate severity of TI after HTx with risk factors
4. identify mechanisms of occurrence of TI after a heart transplantation
5. suggest TI prevention strategies after a heart transplantation.

4.1 Incidence of TI

In this study, incidence of TI was retrospectively examined in 857 of 1515 patients who underwent HTx between 1986 and 2010, survived at least 12 months and had data regarding TI in echocardiographic evaluations.38% n=327 of patients had no TI, 43 % n=369 TI I, 13% n= 109 TI 2, 5% n=42 TI 3 and 1% n=10 TI 4.
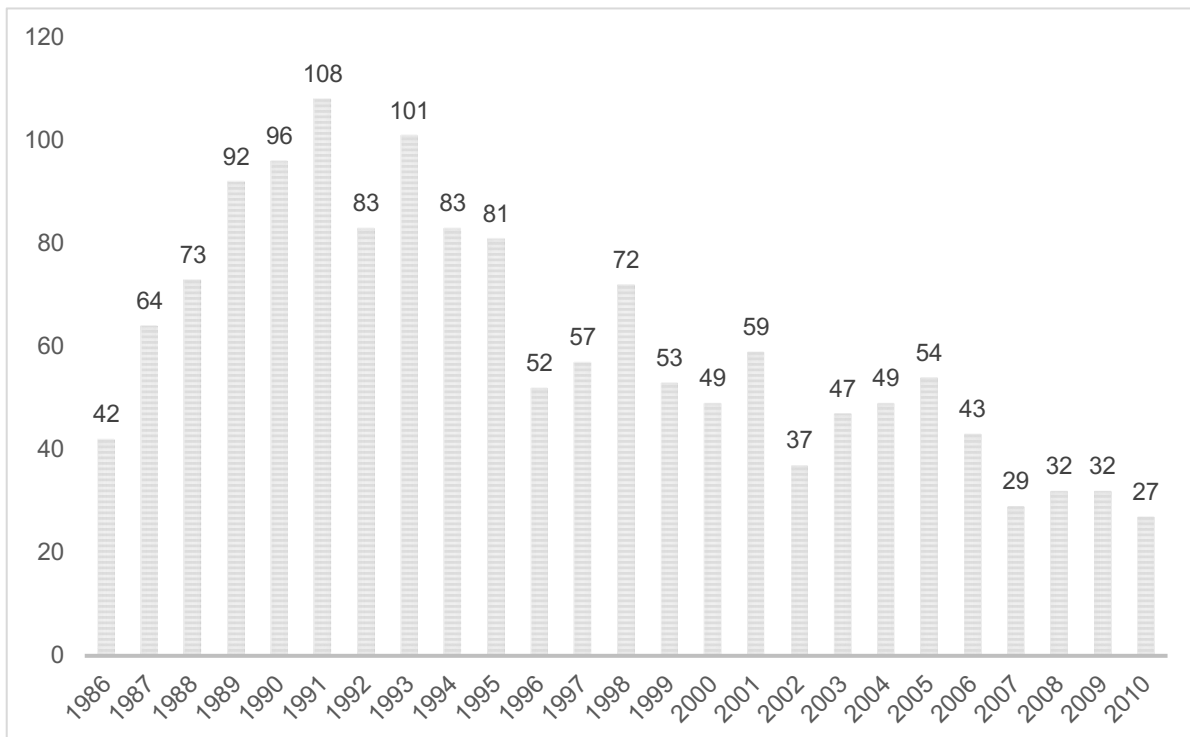
Figure 22 Number of patients per year, transplanted in DHZB between 1986 and 2010

The group of 152 patients (37% n=56 no TI, 43% n=65 TI 1, 12% n= 19 TI 2, 6% n= 9 TI 3, 2% n = 3 TI 4) representing the patient group who underwent HTx between 1986 and 2010 was divided into groups based on the severity of postoperative TI (TI ≤ 2 92, 1% n=140 and TI >2 7.9% n=12. Earlier study reports show that 47% to 98 % were affected by TI, and 70% to 83% of normal subjects had TI, although this was mostly trivial to mild in severity[92]. One study showed more moderate/severe TI in heart transplant patients than in normal subjects

(12% vs 3%, p =0.05)[68]. Williams *et al.* found a 32% prevalence of moderate or severe TI[6]. Huddleston *et al.* found that 10.4% had moderate TI and 10.9% had severe TI[70]. Rees *et al* found 12% of patients had moderate TI and none had severe TI[68]. Lewen *et al.* found that 20% of patients had severe TI and 50% had moderate TI[67]. Hausen *et al.* documented "grade 3" echocardiographic, moderate/severe TI occurring in 50% of patients at 4 years posttransplantation[2]. It is complicated to compare the prevalence of TI after HTx from various studies due to differences in the follow-up period, definitions of significant TI and procedures used to identify TI[37,87]. In the present study, with the biggest cohort of 857 patients, significant TI after HTx is defined as TI greater than moderate (>grade 2) that is of clinical significance and requires conservative or surgical therapy. The average follow-up time in the present study was 9 years.

Table 8 Prevalence, follow-up and definition of TI in different studies

Study	No. of patients	TI prevalence at the end of the follow-up (%)	Average follow-up period (years)	Definition of significant TI
Current study (2017)	n=852	6%	9	> moderate
Berger *et al.*, (2012)	n=163	14.1%	8.2	≥ mild-moderate
Chan *et al.* (2001)	n=336	34%	4.5	≥ moderate
Aziz *et al.* (1999)	n=249	53.9%	5	≥ moderate
Hausen *et al.* (1995)	n=251	50%	4	≥ moderate-severe
Williams *et al.* (1996)	n=72	32%	2.4	≥ moderate
Yankah *et al.* (2000)	n=647	5.5%	5	≥ moderate
Chen *et al.* (2008)	n=178	26.4%	5	≥ moderate
Huddleston *et al.* (1994)	n=183	20%	4	≥ moderate

TI tricuspid insufficiency, n number

4.2 Correlation of TI after HTx with risk factors

The most common cause of TI is dilatation of the right ventricle due to left ventricular failure, mitral stenosis, portal hypertension, pulmonary stenosis or atrial septal defect. The underlying diseases in the majority of cases were DCM (65.6%) and CAD (27.2%). Of the total of 151 respondents only 6.6% were dialyzed; 93.4% of them were not dialyzed.

The findings of the present study revealed that the majority of heart transplanted patients were male (n=130, 85.5%). The results also indicated that there is no association between TI and gender (p =0.686). This finding is in line with the results of retrospective case-control studies by Najib *et al.*, where the findings emphasized that gender has no role in the incidence of TI [102]. When comparing TI and the sex of the recipient, out of 130 males 92.3 % were recorded as having TI ≤2 and 7.7% TI >2, whereas in females, out of 22, 90.9 % with TI ≤2 and 9.1 % with TI >2 were recorded. Hence there is no association between TI and gender of the recipient.

In the present study, univariable analysis revealed that there is a significant difference in TI between different recipient age groups (p=0.027). Patients with TI >2 (mean=42.40) were younger than those with TI ≤2 (mean=49.55). However, this finding is contradicted by the results of Lewen *et al.,* where the age of recipient is an insignificant variable [67]. Sun *et al.* found that the age of the recipient is a significant predictor of acute cardiac allograft rejection [83]. It can indirectly affect TI by the necessity of EMB, the number of which is another significant variable. The study shows no significance of donor age group. The mean age of donors was 35.28 (SD±13.78) years and maximum age was 65 years. Shortage of suitable donors and increasing demand for heart transplantation resulted in the extension of acceptance criteria, specifically the age of donors[103]. Previously, the maximum age limit for donors was 35 years. Due to this the problems associated with older donors increased; they included graft failure, transmission of CAD, valvular degeneration of the donor heart, hypertensive heart disease and so on [104]. In spite of these concerns, due to increase in the demand for transplantation and the limited number of donors, transplants from older donors are increasing.

4.3   Occurrence mechanisms of TI after HTx

4.3.1   Functional TI

The factors which influence the functional TI include geometric distortion, annular ring dilatation, mismatch of donor and recipient pericardial cavity and malcoaptation of valve leaflets. Previous studies have highlighted the importance of preservation of tricuspid annulus

geometry to prevent postoperative TI [15, 18, 74, 80]. The present study analyzed the donor/recipient anterior wall ratio and anterior/septal leaflet excursion ratio to identify the influence of geometric preservation of the annulus of the tricuspid valve. The findings show significance in both cases ($p < 0.001$). Tricuspid annulus anterior/septal leaflet excursion ratios could not be used for multivariable analysis because of the small number of patients with available examination results (n= 98).

De Simone and his team found an essential link between TI and the recipient atrial dimensions and recipient to donor right atrium ratio among the patients who underwent a biatrial cardiac transplantation[15]. Dandel and his team found that the patients without TI had a D/R ratio of < 1, compared to those with severe TI with a D/R ratio of > 1[74].

Changes in atrial and tricuspid annulus geometry after cardiac transplantation are an important mechanism in developing TI after heart transplantation. Our echocardiographic assessments showed that donor/recipient anterior wall ratio >1 correlates with the position of the tricuspid leaflets, which causes TI with an eccentric jet; this is atypical for annular dilatation, which is the main finding in patients with TI who did not undergo cardiac transplantation (Figures 23- 27).
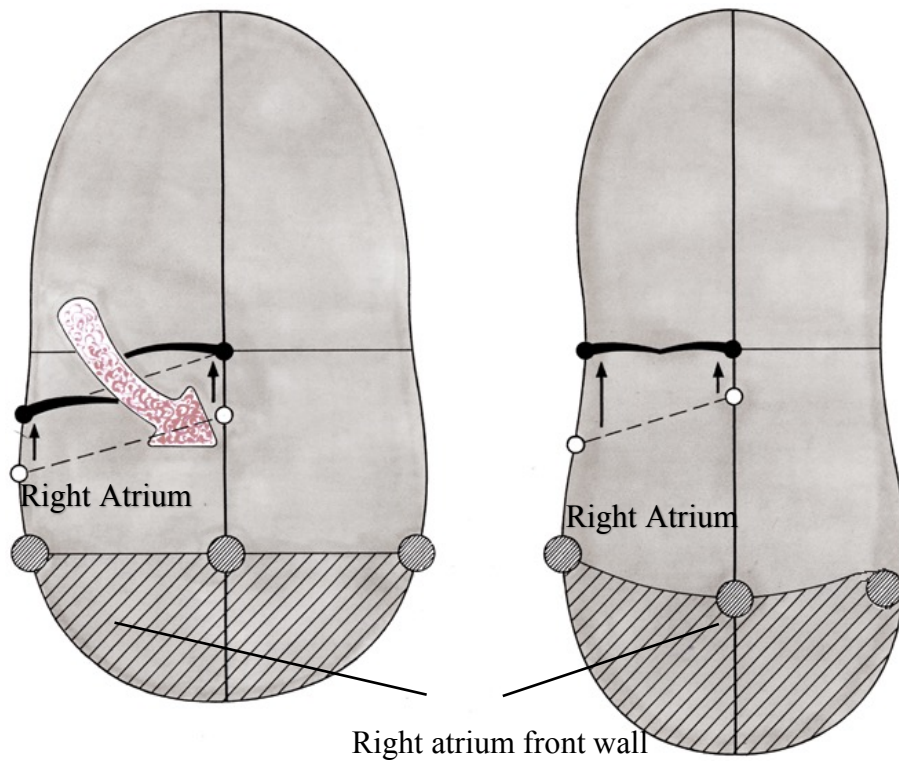
Figure 23 Schematic mechanism of tricuspid valve insufficiency in a heart transplant recipient. Transplanted heart with Donor / Recipient anterior wall ratio >1 in echocardiographic assessments and typical excentric jet, malposition and malcoaptation of valve leaflets due to traction in the right atrium -left, transplanted heart with right Donor / Recipient anterior wall ratio < 1 in echocardiography where no traction present -right
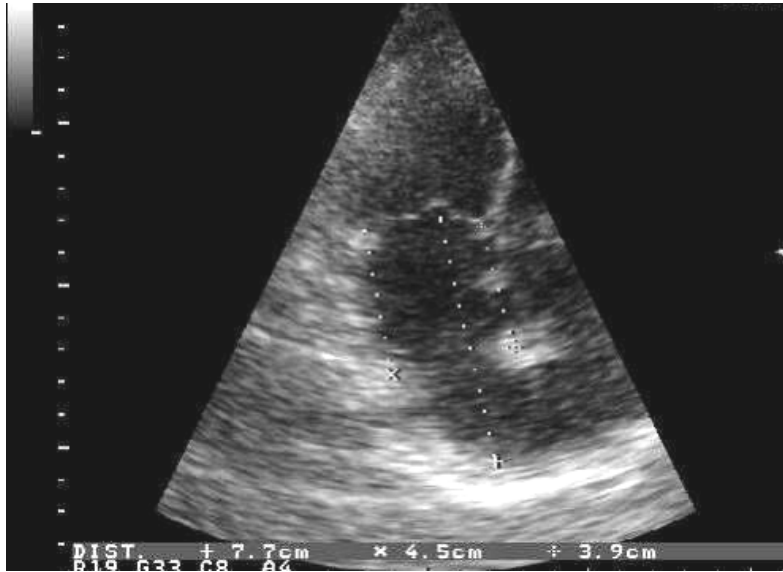
Figure 24 Modified four chamber view of transplanted heart with D/R right atrium anterior wall ratio >1
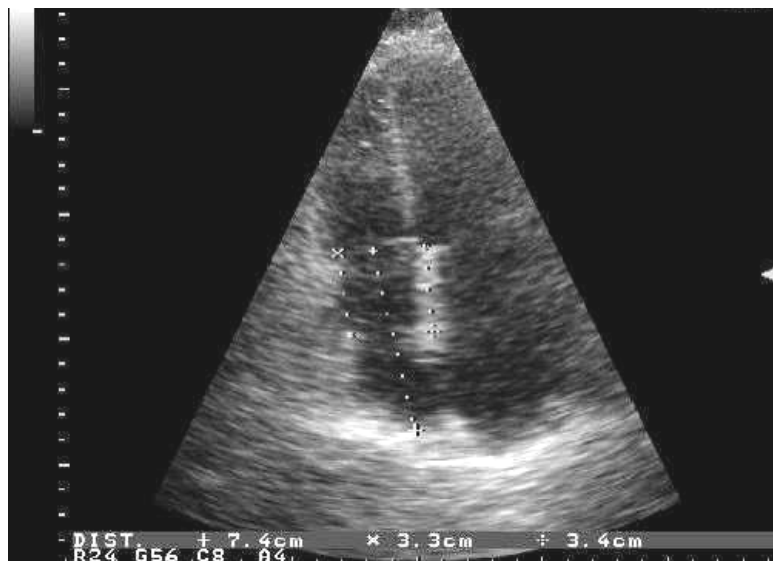
Figure 25 Modified apical four chamber view of transplanted heart with D/R right atrium anterior wall ratio <1
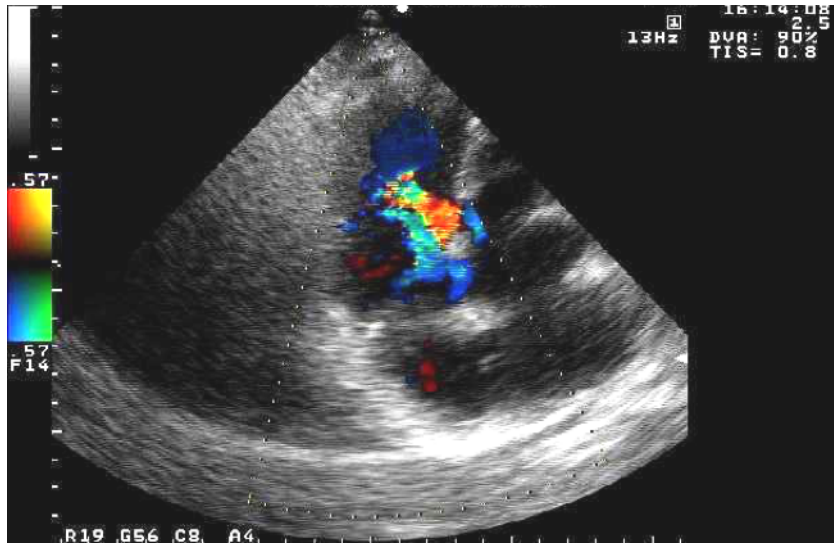
Figure 26 Excentric jet in modified four chamber view of transplanted heart in with D/R right atrium anterior wall ratio >1
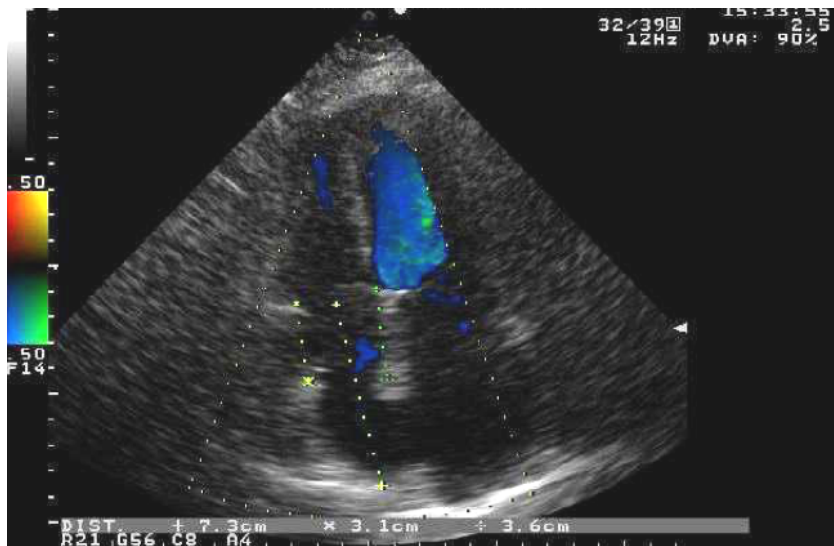
Figure 27 No regurgitant jet in modified four chamber view of transplanted heart with D/R right atrium anterior wall ratio <1

Haverich *et al.* concluded that TI after HTx can occur because of mismatch of donor heart and recipient pericardial cavity[72]. By using multivariable analysis, Hausen *et al.* showed that the weight of the donor heart has an impact on TI after HTx[2]. The present study measured the width of the heart, and the chest on preoperative X-ray and calculated their ratio. These show that there is no significance, but width of chest and heart was bigger in patients with TI >2 (mean 30±3.85, 17.88±2.75 resp.) than those with TI ≤2 (mean 28.9±3.58, 16.43±2.72 resp.) Of the other parameters, weight, BMI, and BSA of donor and recipient show no significance but a trend to significance is shown by the donor-to-recipient BMI ratio ($p=0.080$) and height of recipient ($p=0073$).

Several studies revealed a correlation between TI and pulmonary pressure and reported that early postoperative pulmonary hypertension resolved in most post-transplant patients [2, 18, 67, 87]. Statistical data from other studies such as Lo *et al.*, Aziz *et al.*, Hausen *et al.*, Rees *et al.*, Huddelson *et al.* and Yankah *et al.* indicates that there is no effective association between preoperative SPAP and postoperative TI. In line with these studies, the present study also shows insignificance of preoperative pulmonary pressure [2,18,37,68,69,70].

Del Rizzo et al. showed in their study that organ ischemia time affects survival after cardiac transplantation. Our study, like many others, showed no significance of organ ischemia time for severe TI insufficiency after cardiac transplantation[104].

Dialysis is another pathologic factor that can play a role in atrial size enlargement because of volume overload. Prevalence of TI in patients with end-stage renal disease was found to be 30.6%[59]. It was shown as a risk factor for developing TI after HTx in two studies[67, 72]. Kim et al. reported a case of spontaneous chordae rupture and shortened papillary muscle of the tricuspid valve of a patient on dialysis[105]. Even though only 10 patients of 152 were dialyzed, it showed significance ($p=0.026$). The effect of Dialysis on TI after HTx can be explained by changes in tricuspid valve anatomy and volume overload that worsen the grade of TI.

Morgan and Edward reviewed 39 studies and compared consequences of three anastomosis techniques. They concluded that bicaval techniques provide more functional advantage, such as reduced valvular insufficiency, than others. However, this study did not reveal any significant difference in early and later TI or rate of TI progression [71]. Another

study by Yankah *et al.* reported that execution of the Lower and Shumway technique facilitated low TI incidence after orthotopic transplantation in 1,124 patients at the Deutsches Herzzentrum Berlin. Marelli *et al.* recommended the modified bicaval technique by attachment of a triangular flap of the recipient's right atrial tissue to the anterior aspect of the native inferior vena cava remnant[37,51].

4.3.2 Anatomic TI

The EMB is a most important cause of anatomic disruption of the valve apparatus such as torn leaflet or ruptured chordae tendineae, severe prolapse or flail valve [17]. Many studies have emphasized the importance of EMB on development of TI[2, 6, 37, 70, 75, 76, 78]. The patient's clinical condition, the operator's experience, access sites and type of bioptome used have an influence on TI when EMB is taken[77]. Aziz *et al.* found a significant relationship between rejection > grade 2 and total number of biopsies[18]. The importance of number of biopsies was shown also by Marelli *et al.,* Nguyen *et al.*, Fiorelli *et al* [90, 93, 106]. Berger *et al.* concluded that TI after HTx can be related to graft vasculopathy[87].

All patients received classic triple immunosuppressive therapy. Since 1992, rejection has been monitored in our clinic non-invasively with telemetric intramyocardial electrocardiography based on day-by-day changes in the maximal amplitude of the QRS-complex. Only in doubtful IMEG and echocardiographic data is endomyocardial biopsy done. Before this protocol came into effect, endomyocardial biopsy was used. The current study revealed that there is no significant correlation of occurrence of TI >2 with the highest biopsy grade, number of biopsies with more than moderate grade, cardiac allograft microvasculopathy or organ ischemia time but there was significance in the number of biopsies (p=0.003), using univariable analysis. The multivariable analysis in the present study showed that donor recipient anterior wall ratio, number of biopsies performed and dialysis have independent significance for TI after cardiac transplantation.

In our study, the total number of biopsies showed significance with mean value of 9.11 (SD ±2.72) and 26.92 (SD± 22.94) in the TI ≤2 and T >2 group in univariate analysis, respectively. Patients with known etiology of TI caused by perforated or torn leaflet and ruptured chordae during EMB were excluded. Significant correlation between TI development and number of biopsies was identified also by Hausen *et al.*[2]. A similar result was noted by

Nguyen *et al.* and Lo *et al.*[69,90]. Fiorelli *et al.* found tricuspid valve tissue in 12 (2.9%) of 417 patients after an EMB. TI was increased in two of these cases afterwards (2/12; 16.7%) [106] The mechanism of developing TI after HTx due to number of biopsies can be explained by microscopic damage and changes in the structure of the valve apparatus which are not detectable at the time of echocardiographic evaluation and have a cumulative character. The microscopic changes on tricuspid valve apparatus of transplanted heart after EMB should be further investigated.

4.4 Preventi**o**n and therapy of TI after a heart transplantation.

4.4.1 Therapy modalities

4.4.1.1 Ultrafiltration

Patients with functional TI and end-stage renal disease requiring dialysis could be treated using intensified ultrafiltration. Cirit *et al.* showed disappearance or reduction of TI in patients with end stage renal disease using intensified, aggressive ultrafiltration and discontinuing antihypertensive drugs[107].

4.4.1.2 Surgical technique

The present findings and literature show that preservation of long recipient RA anterior wall segments using the standard biatrial or bicaval anastomosis technique (D/R <1) and abundant lateral donor atrial length in comparison to the septal length is essential for prevention of TI[1].

Modified inferior vena cava anastomosis with bicaval technique anastomosis or generous atrial cuff with standard biatrial technique can be used to reduce the tension between anastomoses[1, 51]. Reduction of the pericardial closure could be suggested in recipients with a large pericardial cavity[37, 72].

The objective of tricuspid restoration is to decrease annular dilatation and reduce tricuspid valve leaflet binding. Methods generally used are supple rings, bands or inflexible adapting rings, suture annuloplasties , bicuspidization, limited purse-string (De Vega),

adapted De Vega, pericardial annuloplasty, edge-to-edge "clover" method by stitching the free edges of tricuspid leaflets in combination with ring annuloplasty and frontal tricuspid leaflet expansion [108-113].

To prevent TI, prophylactic tricuspid valve annuloplasty has been used in both the standard biatrial and bicaval technique[98, 99]. Although results are encouraging, prophylactic annuloplasty poses risks such as infection, additional procedure at the time of HTx and possible iatrogenic injury to structures such as the atrioventricular node. Because of these, it should be applied selectively.

4.4.2 Diagnostic modalities

Echocardiographically detected anomalies were revealed by the study to have a link with post-transplant rejection episodes such as the decreased tissue, ejection fraction, Doppler velocity, stroke volume, increased pericardial effusion and posterior wall thickness; shortened isovolumic relaxation time; mitral inflow E/A ratio >1.7; inferior vena cava diameter; and duration of pulmonary vein atrial reversal[82, 83]. In short, the study was able to determine the anomalies behind the health condition and the ratio of patients who were prone to such conditions.

Daily intramyocardial electrocardiography observation is always considered as an alternative regimen to rejection monitoring[36]. It was used by Yankah and his team of researchers, who performed EMBs with a 45-cm sheath bioptome only in cases of patients with doubtful IMEG and echocardiographic data and at times of annual routine heart catheterization. The group reported that only 16 (2.5%) of 647 patients with severe TI required surgical correction[37]. After the application of IMEG, the group performed only 4.8 biopsies on a single patient in 1 year. This, in conjunction with the long bioptome sheath used, was suggested to account for the lower-than-expected rate of severe TI.

Usage of a longer sheath at the time of biopsy allows the bioptome to be advanced beyond the tricuspid valve with minimal probability of damaging it. It has been shown that using a 45-cm sheath reduces prevalence of damaged tricuspid leaflet and mean grade of TI[6].

One of the non-invasive methods tested is the AlloMap test. By using real-time polymerase chain reaction technology, scores based on expression of 20 genes can be generated. The scores have been shown to differ between mild and moderate/severe acute cellular rejection in the cardiac allograft rejection gene expression study [114,115].

4.5 Limitations

It is to be acknowledged that the current study has certain limitations:

- by its nature, it is subject to the restrictions of a retrospective study,
- due to the long period in which the study patients were treated, the population is certainly heterogeneous due to time effects,
- the severity of TI was graded by measuring the regurgitant jet area size on color Doppler. The major limitation of this grading is that it does not yield quantitative data.

5 Conclusion

After heart transplantation, TI is common and the incidence of severe TI increases with time. At the time of diagnosis, most patients even with severe TI are asymptomatic; however, symptoms will often progress over time and some patients may require TVR for refractory symptoms.

Apart from this, transplanting hearts from older donors remains inadvisable. However, the shortage of suitable donors and the increasing demand for heart transplantation has resulted in the extension of acceptance criteria, specifically in terms of the age of the donor.

The present study showed no significance in terms of recipient gender, basic disease, recipient weight, recipient body mass index, recipient body surface area, pre-operative pulmonary arterial pressure, donor organ ischemia time, donor gender, donor age, donor height, donor weight, donor body mass index (BMI), donor body surface area (BSA), chest X-ray thorax width, chest X-ray heart width, chest X-ray thorax/heart ratio, highest rejection grade on biopsy or degree of cardiac allograft microvasculopathy.

The significance of right atrium to front wall ratio and dialysis in multivariable analysis, significance of tricuspid annulus anterior to septal leaflet excursion in univariable analysis and trend to significance of such factors as BMI donor to recipient ratio gives us reason to conclude that preservation of the tricuspid annulus geometry is an important risk factor for avoiding TI after HTx. It could be prevented using modified inferior vena cava anastomosis with bicaval technique anastomosis or generous atrial cuff with standard biatrial technique [37,51]. Development of TI can be treated using different tricuspid valve reconstruction techniques or by pericardial reduction[72].

The number of biopsies is also a major risk factor for TI. It is advisable to utilize non-invasive diagnostic modalities to reduce the number of EMB in order to prevent TI after HTx.

6 References

1.   C. Knosalla MD, I. Schmitt-Knosalla , R. Yeter , R. Hetzer. Impact of Surgical Techniques on Long-Term Results after Heart Transplantation. Thorac cardiovasc Surg. 2009;57:159-61.

2.   Hausen B, Albes JM, Rohde R, Demertzis S, Mugge A, Schafers HJ. Tricuspid valve regurgitation attributable to endomyocardial biopsies and rejection in heart transplantation. Ann Thorac Surg. 1995;59(5):1134-40.

3.   Urbanowicz T, Michalak M, Kociemba A, Straburzynska-Migaj E, Katarzynski S, Grajek S, Jemielity M. Predictors of Tricuspid Valve Anulus Dilation in a Heart Recipient Population. Transplant Proc. 2016;48(5):1742-5.

4.   Anderson CA, Shernan SK, Leacche M, Rawn JD, Paul S, Mihaljevic T, Jarcho JA, Stevenson LW, Fang JC-T, Lewis EF, Couper GS, Mudge GH, Byrne JG. Severity of intraoperative tricuspid regurgitation predicts poor late survival following cardiac transplantation. Ann Thorac Surg. 2004;78(5):1635-42.

5.   Wartig M, Tesan S, Gabel J, Jeppsson A, Selimovic N, Holmberg E, Dellgren G. Tricuspid regurgitation influences outcome after heart transplantation. J Heart Lung Transplant. 2014;33(8):829-35.

6.   Williams MJ, Lee MY, DiSalvo TG, J. Biopsy-induced flail tricuspid leaflet and tricuspid regurgitation following orthotopic cardiac transplantation. Am J Cardiol. 1996;77:1339-44.

7.   Grande AM, Rinaldi M, D'Armini AM, Campana C, Traversi E, Pederzolli C, Abbiate N, Klersy C, Viganò M. Orthotopic heart transplantation: standard versus bicaval technique. Am J Cardiol. 2000;85(11):1329-33.

8.   Talha S, Charloux A, Piquard F, Geny B. Brain natriuretic peptide and right heart dysfunction after heart transplantation. Clin Transplant. 2017;31(6).

9.   Aziz TM, Saad RA, Burgess MI, Campbell CS, Yonan NA, J. Clinical significance of tricuspid valve dysfunction after orthotopic heart transplantation. J Heart Lung Transplant. 2002;21:1101-8.

10.   Alharethi R, Bader F, Kfoury AG, Hammond ME, Karwande SV, Gilbert EM, Doty DB, Hagan ME, Thomas H, Renlund DG. Tricuspid valve replacement after cardiac transplantation. J Heart Lung Transplant. 2006;25(1):48-52.

11.   Raghavan R, Cecere R, Cantarovich M, Giannetti N. Tricuspid valve replacement after cardiac transplantation. Clin Transplant. 2006;20(6):673-6.

12.   Anderson C, Filsoufi F, Farivar RS, Adams DH. Optimal management of severe tricuspid regurgitation in cardiac transplant recipients. J Heart Lung Transplant. 2001;20(2):247.

13.   Filsoufi F, Salzberg SP, Anderson CA, Couper GS, Cohn LH, Adams DH. Optimal surgical management of severe tricuspid regurgitation in cardiac transplant patients. J Heart Lung Transplant. 2006;25(3):289-93.

14.   Dandel M, Hummel M, Loebe M, J. Right atrial geometry and tricuspid regurgitation after orthotopic heart transplantation: benefits of a modified biatrial surgical technique. J Heart Lung Transplant. 2001;20:246-7.

15.   Simone R, Lange R, Sack RU, Mehmanesh H, Hagl S. De Atrioventricular valve insufficiency and atrial geometry after orthotopic heart transplantation. Ann Thorac Surg. 1995;60:1686-93.

16.   Birnbaum J, Ulrich SM, Schramm R, Hagl C, Lehner A, Fischer M, Haas NA, Heineking B. Transient severe tricuspid regurgitation after transplantation of an extremely oversized donor heart in a child-Does size matter? A case report. Pediatr Transplant. 2017;21(1).

17.   Wong RC-C, Abrahams Z, Hanna M, Pangrace J, Gonzalez-Stawinski G, Starling R, Taylor D. Tricuspid regurgitation after cardiac transplantation: an old problem revisited. J Heart Lung Transplant. 2008;27(3):247-52.

18. Aziz TM, Burgess MI, Rahman AN, Campbell CS, Deiraniya AK, Yonan NA. Risk factors for tricuspid valve regurgitation after orthotopic heart transplantation. Ann Thorac Surg. 1999;68:1247-51.

19. Lower RR, Shumway NE. Studies on orthotopic homotransplantation of the canine heart. Surg Forum. 1960;11:18-9.

20. Barnard CN. The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. S Afr Med J. 1967;41(48):1271-4.

21. Kirklin JW, Kouchoukos NT. Kirklin/Barratt-Boyes cardiac surgery : morphology, diagnostic criteria, natural history, techniques, results, and indications. 3rd ed. Philadelphia, Pa.: Churchill Livingstone; 2003.

22. Caves PK, Stinson EB, Billingham M, Shumway NE. Percutaneous transvenous endomyocardial biopsy in human heart recipients. Ann Thorac Surg 1973;16:325-36.

23. Borel JF. History of the discovery of cyclosporin and of its early pharmacological development. Wien Klin Wochenschr. 2002;114(12):433-7.

24. Stelken AM, Younis LT, Jennison SH, Miller DD, Miller LW, Shaw LJ, Kargl D, Chaitman BR. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. J Am Coll Cardiol. 1996;27(2):345-52.

25. Rothenburger M, Wichter T, Schmid C, Stypmann J, Tjan TD, Berendes E, Etz C, Pioux A, Loher A, Wenzelburger F, Drees G, Hoffmeier A, Breithardt G, Scheld HH. Aminoterminal pro type B natriuretic peptide as a predictive and prognostic marker in patients with chronic heart failure. J Heart Lung Transplant. 2004;23(10):1189-97.

26. Myers J, Gullestad L, Vagelos R, Do D, Bellin D, Ross H, Fowler MB. Cardiopulmonary exercise testing and prognosis in severe heart failure: 14 mL/kg/min revisited. Am Heart J. 2000;139(1 Pt 1):78-84.

27.   Cohn JN, Johnson GR, Shabetai R, Loeb H, Tristani F, Rector T, Smith R, Fletcher R. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. Circulation. 1993;87(6 Suppl):VI5-16.

28.   Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. Circulation. 1993;87(6 Suppl):VI40-8.

29.   Cimato TR, Jessup M. Recipient selection in cardiac transplantation: contraindications and risk factors for mortality. J Heart Lung Transplant. 2002;21(11):1161-73.

30.   Frantz RP, Olson LJ. Recipient selection and management before cardiac transplantation. Am J Med Sci. 1997;314(3):139-52.

31.   Baldwin JC, Anderson JL, Boucek MM, Bristow MR, Jennings B, Ritsch ME, Jr., Silverman NA. 24th Bethesda conference: Cardiac transplantation. Task Force 2: Donor guidelines. J Am Coll Cardiol. 1993;22(1):15-20.

32.   Tischler MD, Lee RT, Plappert T, Mudge GH, St John Sutton M, Parker JD. Serial assessment of left ventricular function and mass after orthotopic heart transplantation: a 4-year longitudinal study. J Am Coll Cardiol. 1992;19(1):60-6.

33.   Gerber BL, Bernard X, Melin JA, Delestinne T, Vanbutsele R, Goenen M, Vanoverschelde JL. Exaggerated chronotropic and energetic response to dobutamine after orthotopic cardiac transplantation. J Heart Lung Transplant. 2001;20(8):824-32.

34.   Murali S, Uretsky BF, Armitage JM, Tokarczyk TR, Betschart AR, Kormos RL, Stein KL, Reddy PS, Hardesty RL, Griffith BP. Utility of prostaglandin E1 in the pretransplantation evaluation of heart failure patients with significant pulmonary hypertension. J Heart Lung Transplant. 1992;11(4 Pt 1):716-23.

35. Caves P, Coltart J, Billingham M, Rider A, Stinson E. Transvenous endomyocardial biopsy--application of a method for diagnosing heart disease. Postgrad Med J. 1975;51(595):286-90.

36. Knosalla C, Grauhan O, Muller J, Pfitzmann R, Fietze E, Cohnert T, Volk HD, Hetzer R. Intramyocardial electrogram recordings (IMEG) for diagnosis of cellular and humoral mediated cardiac allograft rejection. Ann Thorac Cardiovasc Surg. 2000;6(2):89-94.

37. Yankah AC, Musci M, Weng Y, J. Tricuspid valve dysfunction and surgery after orthotopic cardiac transplantation. Eur J Cardiothorac Surg. 2000;17:343-8.

38. Dandel M, Hummel M, Muller J, Wellnhofer E, Meyer R, Solowjowa N, Ewert R, Hetzer R. Reliability of tissue Doppler wall motion monitoring after heart transplantation for replacement of invasive routine screenings by optimally timed cardiac biopsies and catheterizations. Circulation. 2001;104(12 Suppl 1):I184-91.

39. Muller J, Eubel A, Dandel M, Hummel M, Hetzer R. [Non-invasive monitoring of rejection after cardiac transplantation. The method and retrospective analysis of data on 734 patients]. Dtsch Med Wochenschr. 2001;126(44):1223-8.

40. Billingham ME, Cary NR, Hammond ME, J. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. J Heart Transplant. 1990;9:587-93.

41. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, Andersen CB, Angelini A, Berry GJ, Burke MM, Demetris AJ, Hammond E, Itescu S, Marboe CC, McManus B, Reed EF, Reinsmoen NL, Rodriguez ER, Rose AG, Rose M, Suciu-Focia N, Zeevi A, Billingham ME. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant. 2005;24(11):1710-20.

42. Winters GL, Marboe CC, Billingham ME, J. The International Society for Heart and Lung Transplantation grading system for heart transplant biopsy specimens: clarification and commentary. J Heart Lung Transplant. 1998;17:754-60.

43.   Hertz MI, Aurora P, Christie JD, Dobbels F, Edwards LB, Kirk R, Kucheryavaya AY, Rahmel AO, Rowe AW, Taylor DO. Registry of the International Society for Heart and Lung Transplantation: a quarter century of thoracic transplantation. J Heart Lung Transplant. 2008;27(9):937-42.

44.   Billingham ME. Histopathology of graft coronary disease. J Heart Lung Transplant. 1992;11(3 Pt 2):S38-44.

45.   Ramzy D, Rao V, Brahm J, Miriuka S, Delgado D, Ross HJ. Cardiac allograft vasculopathy: a review. Can J Surg. 2005;48(4):319-27.

46.   Hiemann NE, Wellnhofer E, Knosalla C, Lehmkuhl HB, Stein J, Hetzer R, Meyer R. Prognostic impact of microvasculopathy on survival after heart transplantation: evidence from 9713 endomyocardial biopsies. Circulation. 2007;116(11):1274-82.

47.   Lower RR, Stofer RC, Shumway NE, J. Homovital transplantation of the heart. Cardiovasc Surg. 1961:196-204.

48.   Cooley DA, Bloodwell RD, Hallman GL, Leachman RD, Nora JJ, Milam JD. Cardiac transplantation: general considerations and results. Ann Surg. 1969;169(6):892-905.

49.   Fraund S, Rahimi A, Hirt S, Schöneich F, Böning A, Cremer J. Alternative technique of the right atrial anastomosis (cavo-atrial) in orthotopic heart transplantation. Ann Thorac Surg. 2006;81(1):381-2.

50.   Sievers HH, Weyand M, Kraatz EG, Bernhard A. An alternative technique for orthotopic cardiac transplantation, with preservation of the normal anatomy of the right atrium. Thorac Cardiovasc Surg. 1991;39(2):70-2.

51.   Marelli D, Silvestry SC, Zwas D, Inst J. Modified inferior vena caval anastomosis to reduce tricuspid valve regurgitation after heart transplantation. Heart Inst J. 2007;34:30-5.

52.   Sarsam MA, Campbell CS, Yonan NA, Deiraniya AK, Rahman AN, J. An alternative surgical technique in orthotopic cardiac transplantation. J Card Surg. 1993;8:344-9.

53.   Cohn LH, Edmunds LH. Cardiac surgery in the adult. 3rd ed. New York: McGraw-Hill Medical; 2008. 1111-24, 539-570 p. p.

54.   Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, Hagendorff A, Monin J-L, Badano L, Zamorano JL, European Association of E. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr. 2010;11(4):307-32.

55.   Schnabel R, Khaw AV, von Bardeleben RS, Strasser C, Kramm T, Meyer J, Mohr-Kahaly S. Assessment of the tricuspid valve morphology by transthoracic real-time-3D-echocardiography. Echocardiography. 2005;22(1):15-23.

56.   Kwan J, Kim GC, Jeon MJ, Kim DH, Shiota T, Thomas JD, Park KS, Lee WH. 3D geometry of a normal tricuspid annulus during systole: a comparison study with the mitral annulus using real-time 3D echocardiography. Eur J Echocardiogr. 2007;8(5):375-83.

57.   Badano LP, Agricola E, Perez de Isla L, Gianfagna P, Zamorano JL. Evaluation of the tricuspid valve morphology and function by transthoracic real-time three-dimensional echocardiography. Eur J Echocardiogr. 2009;10(4):477-84.

58.   Kwan J, Kim G-C, Jeon M-J, Kim D-H, Shiota T, Thomas JD, Park K-S, Lee W-H. 3D geometry of a normal tricuspid annulus during systole: a comparison study with the mitral annulus using real-time 3D echocardiography. Eur J Echocardiogr. 2007;8(5):375-83.

59.   Bozbas H, Altin C, Karacaglar E, Kanyilmaz S, Yildirir A, Muderrisoglu H, Haberal M. The prevalence and types of cardiovascular disease in patients with end-stage renal disease undergoing renal transplantation. Transplant Proc. 2013;45(10):3478-80.

60.   Kim HK, Kim YJ, Park JS, Kim KH, Kim KB, Ahn H, Sohn DW, Oh BH, Park YB, Choi YS. Determinants of the severity of functional tricuspid regurgitation. Am J Cardiol. 2006;98(2):236-42.

61.   Hansing CE, Rowe GG. Tricuspid insufficiency. A study of hemodynamics and pathogenesis. Circulation. 1972;45(4):793-9.

62.   Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MSJ, Stewart WJ, Chamber Quantification Writing G, American Society of Echocardiography's G, Standards C, European Association of E. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63.

63.   Klein AL, Burstow DJ, Tajik AJ, J. Age-related prevalence of valvular regurgitation in normal subjects: a comprehensive color flow examination of 118 volunteers1990. 54-63 p.

64.   Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ, American Society of E. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003;16(7):777-802.

65.   American College of C, American Heart Association Task Force on Practice G, Society of Cardiovascular A, Bonow RO, Carabello BA, Chatterjee K, de Leon AC, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons.   JACC. 2006;48(3):e1-148.

66.   Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A, Task Force on the Management of Valvular Hearth Disease of the European Society of C, Guidelines ESCCfP.

Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J . 2007;28(2):230-68.

67.   Lewen MK, Bryg RJ, Miller LW, Williams GA, Labovitz AJ, J. Tricuspid regurgitation by Doppler echocardiography after orthotopic cardiac transplantation. Am J Cardiol. 1987;59:1371-4.

68.   Rees AP, Milani R, Lavie CJ, Smart FW, Ventura HO. V, Valvular regurgitation and right-sided cardiac pressures in heart transplant recipients by complete Doppler and color flow evaluation. Chest. 1993;104:82-7.

69.   Lo C-Y, Chang H-H, Hsu C-P, Lai S-T, Shih C-C. Endomyocardial biopsy-related tricuspid regurgitation after orthotopic heart transplantation: single-center experience. JCMA. 2007;70(5):185-92.

70.   Huddleston CB, Rosenbloom M, Goldstein JA, Pasque MK. Biopsy-induced tricuspid regurgitation after cardiac transplantation. Ann Thorac Surg. 1994;57:832-6.

71.   Morgan JA, Edwards NM. Orthotopic cardiac transplantation: comparison of outcome using biatrial, bicaval, and total techniques. J Card Surg. 2005;20(1):102-6.

72.   Haverich A, Albes JM, Fahrenkamp G, Wahlers T, Heublein B, J. Schäfers HJ, Intraoperative echocardiography to detect and prevent tricuspid valve regurgitation after heart transplantation. Eur J Cardiothorac Surg. 1991;5:41-5.

73.   Leyh RG, Jahnke AW, Kraatz EG, Sievers HH. Cardiovascular dynamics and dimensions after bicaval and standard cardiac transplantation. Ann Thorac Surg. 1995;59:1495-500.

74.   Dandel M, Hummel M, Loebe M, J. Right atrial geometry and tricuspid regurgitation after orthotopic heart transplantation: benefits of a modified biatrial surgical technique. J Heart Lung Transplant. 2001;20:246-7.

75.   Braverman AC, Coplen SE, Mudge GH, Lee RT, J. Ruptured chordae tendineae of the tricuspid valve as a complication of endomyocardial biopsy in heart transplant patients. Am J Cardiol. 1990;66:111-3.

76.   Tucker PA, Jin BS, Gaos CM, Radovancevic B, Frazier OH, Wilansky S, J. Flail tricuspid leaflet after multiple biopsies following orthotopic heart transplantation: echocardiographic and hemodynamic correlation. J Heart Lung Transplant. 1994;13:466-72.

77.   Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R, American Heart A, American College of C, European Society of C, Heart Failure Society of A, Heart Failure Association of the European Society of C. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. JACC. 2007;50(19):1914-31.

78.   Wiklund L, Caidahl K, Nilsson B, Svensson G, Berglin E. Kjellström C, Tricuspid valve insufficiency as a complication of endomyocardial biopsy. Transpl Int 1992;1:S255-8.

79.   Schnoor M, Schafer T, Luhmann D, Sievers HH. Bicaval versus standard technique in orthotopic heart transplantation: a systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2007;134(5):1322-31.

80.   Angermann CE, Spes CH, Tammen A, J. Anatomic characteristics and valvular function of the transplanted heart: transthoracic versus transesophageal echocardiographic findings. J Heart Transplant. 1990;9:331-8.

81.   Akasaka T, Lythall DA, Kushwaha SS, Yoshida K, Yoshikawa J, Yacoub MH, J. Valvular regurgitation in heart-lung transplant recipients: a Doppler color flow study. J Am Coll Cardiol. 1990;15:576-81.

82.   Sade LE, Sezgin A, Uluçam M, Taymaz S, Simşek V, Tayfun E, Tokel K, Aşlamaci S, Müderrisoğlu H. Evaluation of the potential role of echocardiography in the detection of allograft rejection in heart transplant recipients. Transplant Proc. 2006;38(2):636-8.

83.   Sun JP, Abdalla IA, Asher CR, Greenberg NL, Popović ZB, Taylor DO, Starling RC, Thomas JD, Garcia MJ. Non-invasive evaluation of orthotopic heart transplant rejection by echocardiography. J Heart Lung Transplant. 2005;24(2):160-5.

84.   Akasaka T, Lythall DA, Kushwaha SS, Yoshida K, Yoshikawa J, Yacoub MH, J. Valvular regurgitation in heart-lung transplant recipients: a Doppler color flow study. J Am Coll Cardiol 1990;15:576-81.

85.   Kalra N, Copeland JG, Sorrell VL. Tricuspid regurgitation after orthotopic heart transplantation. Echocardiography. 2010;27(1):1-4.

86.   Park K, Park C, Chun Y, Shin M, Lee K. Y, H, B, S, C. Bicaval anastomosis reduces tricuspid regurgitation after heart transplantation. Asian Cardiovasc Thorac Ann. 2005;13:251-4.

87.   Berger Y, Har Zahav Y, Kassif Y, Kogan A, Kuperstein R, Freimark D, Lavee J. Tricuspid valve regurgitation after orthotopic heart transplantation: prevalence and etiology. J Transplant. 2012;2012:120702.

88.   Sobczyk D, Sadowski J, Kot I. Górkiewicz- [Clinical relevance of tricuspid regurgitation after orthotopic heart transplantation]. Przegląd Lek. Przegląd Lek. 2004;61:733-6.

89.   Sivarajan VB, Chrisant MR, Ittenbach RF, Clark BJ, 3rd, Hanna BD, Paridon SM, Spray TL, Wernovsky G, Gaynor JW. Prevalence and risk factors for tricuspid valve regurgitation after pediatric heart transplantation. J Heart Lung Transplant. 2008;27(5):494-500.

90.   Nguyen V, Cantarovich M, Cecere R, Giannetti N. Tricuspid regurgitation after cardiac transplantation: how many biopsies are too many? J Heart Lung Transplant. 2005;24(7 Suppl):S227-31.

91.   Mielniczuk L, Haddad H, Davies RA, Veinot JP. Tricuspid valve chordal tissue in endomyocardial biopsy specimens of patients with significant tricuspid regurgitation. J Heart Lung Transplant. 2005;24(10):1586-90.

92.   Chan MC, Giannetti N, Kato T, J. Severe tricuspid regurgitation after heart transplantation. J Heart Lung Transplant 2001;20:709-17.

93.   Marelli D, Esmailian F, Al SYW, J. et. Tricuspid valve regurgitation after heart transplantation. Cardiovasc Surg. 2009;6(1):557-1559.

94.   Daniel WG, Herrmann G, Simon R, Lichtlen PR, J. Mügge A, Quantification of tricuspid regurgitation by Doppler color flow mapping after cardiac transplantation. Am J Cardiol. 1990;66:884-7.

95.   Cooley DA, Messmer BJ, Hallman GL, Leachman RD, Rochelle DG. Technique and results of human heart transplantation. Langenbecks Arch Chir. 1969;326(1):5-24.

96.   Shapira Y, Porter A, Wurzel M, Vaturi M, Sagie A, J. Evaluation of tricuspid regurgitation severity: echocardiographic and clinical correlation. J Am Soc Echocardiogr. 1998;11:652-9.

97.   Koch A, Remppis A, Dengler TJ, Schnabel PA, Hagl S, Sack F-U. Influence of different implantation techniques on AV valve competence after orthotopic heart transplantation. Eur J Cardiothorac Surg. 2005;28(5):717-23.

98.   Brown NE, Muehlebach GF, Jones P, Gorton ME, Stuart RS, Borkon AM. Tricuspid annuloplasty significantly reduces early tricuspid regurgitation after biatrial heart transplantation. J Heart Lung Transplant. 2004;23(10):1160-2.

99.   Jeevanandam V, Russell H, Mather P, Furukawa S, Anderson A, Raman J. Donor tricuspid annuloplasty during orthotopic heart transplantation: long-term results of a prospective controlled study. Ann Thorac Surg. 2006;82(6):2089-95; discussion 95.

100.   Schnoor M, Schäfer T, Lühmann D, Sievers HH. Bicaval versus standard technique in orthotopic heart transplantation: a systematic review and meta-analysis.   J Thorac Cardiovasc Surg. 2007;134(5):1322-31.

101.   Fiorelli AI, Filho CAC, Santos RHB. Cardiac transplantation with bicaval anastomosis and prophylactic graft tricuspid annuloplasty. Rev Bras Cir Cardiovasc. 2008;23:7-13.

102.   Najib MQ, Vittala SS, Challa S, Raizada A, Tondato FJ, Lee HR, Chaliki HP. Predictors of severe tricuspid regurgitation in patients with permanent pacemaker or automatic implantable cardioverter-defibrillator leads. Tex Heart Inst J. 2013;40(5):529-33.

103.   Pasic M, Loebe M, Hummel M, Grauhan O, Hofmeister J, Weng Y, Hetzer R. Heart transplantation: a single-center experience. Ann Thorac Surg. 1996;62(6):1685-90.

104.   Rizzo DF, Menkis AH, Pflugfelder PW, J. Del The role of donor age and ischemic time on survival following orthotopic heart transplantation. J Heart Lung Transplant. 1999;18:310-9.

105.   Kim H, Cho YK, Nam CW, Han SW, Hur SH, Kim YN, Kim KB. Spontaneous chordae rupture of tricuspid valve in patient with chronic renal failure. Eur J Echocardiogr. 2008;9(1):58-9.

106.   Fiorelli AI, Coelho GHB, Oliveira JL, Aiello VD, Benvenuti LA, Santos A, Chi A, Tallans A, Igushi ML, Bacal F, Bocchi EA, Stolf NAG. Endomyocardial biopsy as risk factor in the development of tricuspid insufficiency after heart transplantation. Transplant Proc. 2009;41(3):935-7.

107.   Cirit M, Ozkahya M, Cinar CS, Ok E, Aydin S, Akcicek F, Dorhout Mees EJ. Disappearance of mitral and tricuspid regurgitation in haemodialysis patients after ultrafiltration. Nephrol Dial Transplant. 1998;13(2):389-92.

108.   Dreyfus GD, Raja SG, John Chan KM. Tricuspid leaflet augmentation to address severe tethering in functional tricuspid regurgitation. Eur J Cardiothorac Surg

 2008;34(4):908-10.

109.   Ghanta RK, Chen R, Narayanasamy N, McGurk S, Lipsitz S, Chen FY, Cohn LH. Suture bicuspidization of the tricuspid valve versus ring annuloplasty for repair of functional tricuspid regurgitation: midterm results of 237 consecutive patients.   J Thorac Cardiovasc Surg. 2007;133(1):117-26.

110. McCarthy PM, Bhudia SK, Rajeswaran J, Hoercher KJ, Lytle BW, Cosgrove DM, Blackstone EH. Tricuspid valve repair: durability and risk factors for failure. J Thorac Cardiovasc Surg. 2004;127(3):674-85.

111. Navia JL, Nowicki ER, Blackstone EH, Brozzi NA, Nento DE, Atik FA, Rajeswaran J, Gillinov AM, Svensson LG, Lytle BW. Surgical management of secondary tricuspid valve regurgitation: annulus, commissure, or leaflet procedure? J Thorac Cardiovasc Surg. 2010;139(6):1473-82.e5.

112. Fukuda S, Gillinov AM, McCarthy PM, Matsumura Y, Thomas JD, Shiota T. Echocardiographic follow-up of tricuspid annuloplasty with a new three-dimensional ring in patients with functional tricuspid regurgitation. J Am Soc Echocardiogrhy. 2007;20(11):1236-42.

113. Lapenna E, De Bonis M, Verzini A, La Canna G, Ferrara D, Calabrese MC, Taramasso M, Alfieri O. The clover technique for the treatment of complex tricuspid valve insufficiency: midterm clinical and echocardiographic results in 66 patients. Eur J Cardiothorac Surg. 2010;37(6):1297-303.

114. Starling RC, Pham M, Valantine H, Miller L, Eisen H, Rodriguez ER, Taylor DO, Yamani MH, Kobashigawa J, McCurry K, Marboe C, Mehra MR, Zuckerman A, Deng MC, Working Group on Molecular Testing in Cardiac T. Molecular testing in the management of cardiac transplant recipients: initial clinical experience. J Heart Lung Transplant. 2006;25(12):1389-95.

115. Deng MC, Eisen HJ, Mehra MR, Billingham M, Marboe CC, Berry G, Kobashigawa J, Johnson FL, Starling RC, Murali S, Pauly DF, Baron H, Wohlgemuth JG, Woodward RN, Klingler TM, Walther D, Lal PG, Rosenberg S, Hunt S, Investigators C. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. Am J Transpl. 2006;6(1):150-60.

Publications

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Contribution of the author

The contribution of the author for the thesis consists of literature analysis, definition of variables needed for the study, defining study method, sampling all necessary variables, analysis of statistical study results, comparison of results with other studies, drawing conclusions and providing advice concerning the problem.

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Curriculum Vitae

No curriculum vitae are to be included in electronic dissertations for reasons of confidentiality. Although included in the table of contents, this reference should be replaced by the following annotation: "My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

Risk factors of tricuspid insufficiency after cardiac transplantation

Affidavit

"I, Vusal Hajiyev certify under penalty of perjury by my own signature that I have submitted the thesis on the topic "Risk factors of tricuspid insufficiency after cardiac transplantation". I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

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