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## GENEESKUNDE

*master in de biomedische wetenschappen: milieu en gezondheid*

### Masterproef

*Clinical outcomes and analysis of right ventricular function and geometry in patients undergoing tricuspid annuloplasty in addition to mitral valve surgery during complex left-sided heart surgery*

**Promotor :**  
Prof. Dr. Wilfried MULLENS  
Prof. dr. Marie VANDERSTEEN

### Gille Koppers

*Masterproef voorgedragen tot het bekomen van de graad van master in de biomedische wetenschappen , afstudeerrichting milieu en gezondheid*

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## Abbreviations

TVP	tricuspid valve annuloplasty
MVP	mitral valve annuloplasty
MVR	mitral valve replacement
AVP	aortic valve repair
AVR	aortic valve replacement
CABG	coronary artery bypass grafting
TV	tricuspid valve
MV	mitral valve
TA	tricuspid annulus (annular)
TR	tricuspid valve regurgitation
TI	tricuspid insufficiency
MR	mitral valve regurgitation
RA	right atrium
RV	right ventricle (ventricular)
RVFAC	right ventricular fractional area change
RVSI	right ventricular sphericity index
RVEDA	right ventricular end-diastolic area
LV	left ventricle (ventricular)
LVEF	left ventricular ejection fraction
AVN	atrioventricular node
CS	coronary sinus
CVD	cardiovascular diseases
VHD	valvular heart disease
HF	heart failure
CPB	cardiopulmonary bypass
ESC	European Society of Cardiology
AHA	American Heart Association
ACC	American College of Cardiology
ACEi/ARB	angiotensin converting enzyme inhibitor or angiotensin receptor blocking agent

## Abstracts

### **Clinical outcomes in patients undergoing tricuspid valve annuloplasty in addition to mitral valve surgery during complex left-sided heart surgery**

**Background:** Tricuspid valve annuloplasty (TVP) has been advocated to be performed during mitral valve surgery in case of tricuspid annular ( $TA \geq 4$  cm) dilatation or functional tricuspid valve regurgitation ( $TR > 2$ ).

**Objective:** To determine clinical outcomes and their relation to preoperative echocardiographic findings if TVP guidelines are applied in more complex left-sided heart surgery.

**Methods:** Baseline clinical and echocardiographic data of all consecutive mitral valve surgeries during complex left-sided heart surgeries either with (TVP+) or without TVP (TVP-), performed in a tertiary surgical center between 2007-2010, were analyzed. Adverse events (mortality + heart failure hospitalization) were collected.

**Results:** Compared to TVP- ( $n=86$ ), TVP+ ( $n=89$ ) patients had similar baseline characteristics, except for a lower right ventricular fractional area change (RVFAC). TVP+ group had more concomitant aortic valve surgery performed but less coronary artery bypass grafting (CABG) resulting in a trend towards higher EuroSCOREs (14.2% vs. 9.8%,  $p=0.063$ ). Actual 30-day mortality was higher in the TVP+ group (13.5% vs. 4.7%,  $p=0.042$ ) and more adverse events occurred (40.5% vs. 24.4%,  $p=0.024$ , OR: 1.8; 95% CI 1.1-3.1) related to more heart failure episodes (31.2% vs. 16.7%,  $p=0.045$ , OR: 2.1; 95% CI 1.1-4.0). Right ventricular sphericity index (RVSI) was the only preoperative echocardiographic parameter for adverse events.

**Conclusion:** Patients undergoing TVP in case of TA dilatation or functional TR in addition to mitral valve surgery during complex left-sided surgery still have a high risk for adverse events. The extent of preoperative right ventricular remodeling may be predictive of outcome.

## **Analysis of right ventricular function and geometry after tricuspid annuloplasty concomitant with complex left-sided heart surgery**

**Background:** Tricuspid valve repair (TVP) has been advocated concomitantly with left-sided heart surgery in case of severe tricuspid regurgitation (TR) or tricuspid annular (TA) dilatation. Data about changes in right ventricular (RV) function and geometry after this procedure are lacking.

**Objective:** To compare the differential effects of TVP performed because of TA dilatation or significant functional TR on RV size, geometry and function in patients scheduled for complex left-sided heart surgery.

**Methods:** Pre- and postoperative echocardiographical data from 49 consecutive TVP procedures performed during left-sided heart surgery between 2007-2010 in a tertiary surgical center were analyzed. Changes in RV function and geometry were assessed by measuring RV fractional area change (RVFAC) and RV end-diastolic sphericity index (RVSI =RV long-axis length/ RV short-axis width) at baseline and follow-up.

**Results:** All patients underwent TVP in addition to left-sided heart surgery (96% mitral valve surgery, 31% aortic valve replacement and 35% coronary artery bypass grafting), either because of more than moderate coexistent TR (35%) or because of TA dilatation (diameter >40 mm or 21 mm/m<sup>2</sup>) despite absence of significant TR (65%). At an average follow-up of 3.5 months post-surgery, a favorable change in RV geometry was observed (RVSI increased from  $1.75 \pm 0.24$  to  $1.97 \pm 0.25$ ;  $p < 0.001$ ) despite a non-significant decline in RV systolic function (RVFAC decreased from  $36.2 \pm 12.51\%$  to  $33.02 \pm 11.99\%$ ,  $p = 0.1$ ). Post-TVP, patients with more severe preoperative TR experienced more extensive RV reverse remodeling compared to those with TA dilatation but lesser degrees of TR ( $p = 0.02$  for the change in RV diastolic size and RVSI at follow-up). No difference between both groups was noted for the postoperative change in RVFAC ( $p = ns$ ). In a multivariable analysis, older age and higher preoperative RVFAC were found as independent predictors of a postoperative decrease in RVFAC.

**Conclusion:** In patients undergoing TVP in addition to left-sided heart surgery, the extent of RV remodeling depends on the severity of TR prior to surgery. TVP because of TA dilatation rather than TR results in a favorable change in RV geometry, although RV size may not decrease shortly after the procedure. Although overall RVFAC appears unchanged postoperatively, longer follow-up using more sophisticated parameters than RVFAC may be necessary to evaluate the exact effect of TVP on RV systolic function.

## **Klinische outcomes in patiënten na tricuspidplastie, gelijktijdig uitgevoerd met mitraalplastie tijdens complexe linkszijdige hartchirurgie.**

**Achtergrond:** Voorafgaand onderzoek heeft aangetoond dat tricuspidplastie gelijktijdig met een mitralisplastie ten eerste is aangewezen in geval van tricuspid annulus (TA) dilatatie ( $TA \geq 4$  cm) en/of functionale tricuspid insufficiëntie (TI:  $TR > 2$ ).

**Doel:** Klinische outcomes en hun relatie tot preoperatieve echografische parameters bepalen wanneer tricuspidplastie gelijktijdig met complexe linkszijdige ingrepen wordt uitgevoerd.

**Methoden:** Preoperatieve klinische en echocardiografische gegevens van alle opeenvolgende mitralisklep operaties tijdens complexe linkszijdige hartchirurgie met (TVP+) of zonder tricuspidplastie (TVP-), uitgevoerd in een tertiair chirurgisch centrum tussen 2007-2010, werden geanalyseerd. Adverse events (mortaliteit + hartfalen opname) werden verzameld.

**Resultaten:** Behalve een lagere rechter ventriculaire fractionele verandering, hebben de TVP+ patiënten ( $n=89$ ) in vergelijking met de TVP- patiënten ( $n=86$ ) gelijkaardige preoperatieve karakteristieken. De TVP+ groep onderging wel meer gelijktijdige aortaklep chirurgie maar minder coronaire bypass operaties wat resulteerde in een trend naar hogere EuroSCOREs (14,2% vs. 9,8%,  $p=0,063$ ). De effectieve 30-dagen mortaliteit was hoger in de TVP+ groep (13,5% vs. 4,7%,  $p=0,042$ ) samen met een hoger aantal vastgestelde adverse events (40,5% vs. 24,4%,  $p=0,024$ , OR: 1,8; 95% CI 1,1-3,1), gerelateerd aan opmerkelijk meer hartfalen episodes (31,2% vs. 16,7%,  $p=0,045$ , OR: 2,1; 95% CI 1,1-4,0). Daarnaast was de rechter ventriculaire sfericiteits index de enige preoperatieve echocardiografische parameters voor adverse events.

**Conclusie:** Tricuspidplastie uitgevoerd, in geval van TA dilatatie of functionale tricuspid insufficiëntie, tijdens complexe linkszijdige hartchirurgie leidt tot een hoger risico op adverse events. Mogelijk is de mate van preoperatief rechter ventrikel remodeling een predictieve parameter voor de outcome.



## **Rechter ventrikel en geometrische analyse na tricuspidplastie, gelijktijdig uitgevoerd met complexe linkszijdige hartchirurgie.**

**Achtergrond:** Het is aangewezen om tricuspidplastie (TVP) gelijktijdig uit te voeren met mitralisplastie in geval van tricuspid annulus (TA) dilatatie ( $TA \geq 4$  cm) en/of functionele tricuspid insufficiëntie (TI:  $TR > 2$ ). Gegevens over rechter ventrikel functie en geometrie na deze procedure ontbreken voorlopig nog.

**Doel:** Het effect van tricuspidplastie, in geval van TA dilatatie en/of functionele TI, op de rechter ventrikel grootte, geometrie en functie nagaan in patiënten die complexe linkszijdige hartchirurgie ondergaan.

**Methoden:** Pre- en postoperative echocardiografische gegevens van 49 opeenvolgende TVP procedures, gelijktijdig uitgevoerd met linkszijdige hartchirurgie in een tertiair chirurgisch centrum tussen 2007-2010, werden geanalyseerd. Verandering in rechter ventrikel (RV) functie en geometrie werden geschat door pre- en postoperatief de RV fractionele verandering (RVFAC) en sfericiteits index ( $RVSI = RV \text{ lange-as lengte} / RV \text{ korte-as breedte}$ ) te meten.

**Resultaten:** Alle patiënten ondergingen tricuspidplastie gelijktijdig met linkszijdige hartchirurgie (96% mitralisklep operaties, 31% aortaklep vervangingen (AVR) en 35% coronaire bypass operaties (CABG)), omwille van de aanwezigheid van matig TR (35%) of van TA dilatatie (diameter  $> 40$  mm of  $21 \text{ mm/m}^2$ ) ondanks de afwezigheid van TR (65%). Na een gemiddelde follow-up van 3,5 maanden werd een positieve verandering in RV geometry waargenomen ( $RVSI$  daalde van  $1,75 \pm 0,24$  tot  $1,97 \pm 0,25$ ;  $p < 0,001$ ) desondanks een niet significante daling in de RV systolische functie ( $RVFAC$  daalde van  $36,2 \pm 12,51\%$  tot  $33,02 \pm 11,99\%$ ,  $p = 0,1$ ). Post-TVP, ondervonden patiënten met ernstiger preoperatief TR meer uitgesproken positieve RV remodeling in vergelijking met patiënten met minder preoperatief TR of TA dilatatie ( $p = 0,02$ ). Geen significant verschil in postoperatieve verandering in  $RVFAC$  was waargenomen tussen beide groepen ( $p = ns$ ). In een multivariabele analyse werden oudere leeftijd en hogere preoperatieve  $RVFAC$  gevonden als onafhankelijke predictoren van een postoperatieve daling in  $RVFAC$ .

**Conclusie:** In patiënten die TVP gelijktijdig met linkszijdig hartchirurgie ondergaan is de mate van RV remodeling postoperatief afhankelijk van de preoperatieve graad van TR. TVP uitgevoerd omwille van TA dilatatie zonder ernstig TR leidt eveneens tot positieve RV remodeling, althans is er postoperatief geen verkleining van het RV zoals bij patiënten waarbij de TVP wordt uitgevoerd omwille van  $TR > 2$ . Langere follow-up met meer gesofisticeerde parameters dan  $RVFAC$  is aangewezen om het exacte effect van TVP op de RV systolische functie na te gaan.

# 1. Introduction

## 1.1 The tricuspid valve

Cardiovascular diseases (CVD) are considered worldwide as big killers, it already kills more people in Europe than any other single cause of death. Heart disease, or cardiovascular disease, accounts for 29 percent of deaths worldwide according to the World Health Organization, not to mention the millions of people treated in hospitals for CVD every year which costs the economy billions of Euros annually (1). Although valvular heart disease (VHD) is less frequent than coronary disease or heart failure (HF), it causes significant mortality and morbidity. An estimated 20,891 patients died as a result of VHD in the United States in 2007 (2). Tricuspid valve (TV) disease in particular affects 0.8% of the general population in the United States (3,4).

The cardiac valves are responsible for moving the blood in the right direction through the heart. The tricuspid valve, also called the right-sided atrioventricular valve, regulates the opening between the right atrium (RA) and the right ventricle (RV) (Figure 1). As the right ventricle relaxes during diastole, and the pressure within the right ventricle is lower than the pressure in the right atrium, the tricuspid valve opens and

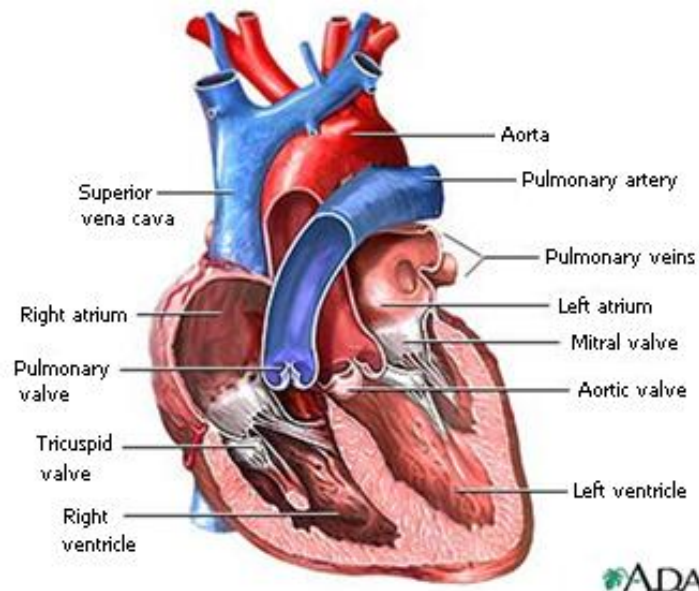
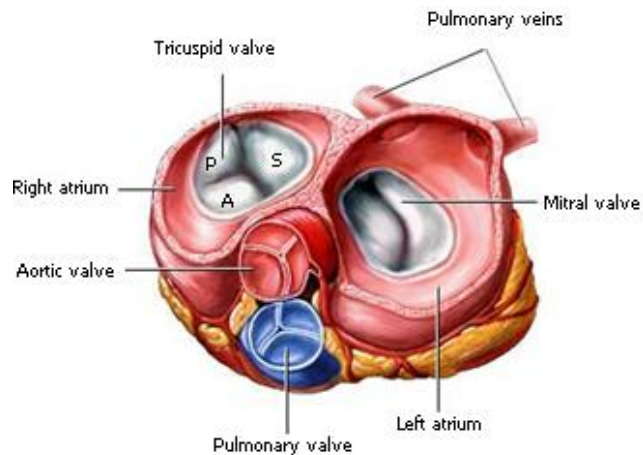


Figure 1: Normal heart structure (5).

blood will flow from the right atrium to the right ventricle. Afterwards, the right atrium will contract allowing more blood to eject into the right ventricle. After contraction of the atrium, the tricuspid valve closes, whereby preventing a backwash of blood ("regurgitation") into the right atrium during the systolic phase of the heart cycle. The mitral valve (MV) regulates the opening between the left atrium and the left ventricle (LV) in a similar manner as the TV. When the pressure in the ventricles during systole becomes higher than the pressure in the pulmonary artery and aorta, the pulmonary and aortic valve open and guide the blood to the lungs and the rest of the body, respectively. After contraction of the ventricles, the pressure drops and the pulmonary and aortic valve close.



ADAM.

Figure 2: Cardiac valves, superior view. Tricuspid valve on the left with A: anterior leaflet, P: posterior leaflet and S: septal leaflet (6).

The tricuspid valve is composed of three leaflets (an anterior, a posterior and a septal leaflet), the chordae tendinae, two discrete papillary muscles, the fibrous tricuspid annulus, and the right atrial and right ventricular myocardium (Figures 1 and 2). The anterior leaflet and the septal leaflet are the largest, whereas the posterior leaflet is notable for the presence of multiple scallops. TV commissures represent the border between the different leaflets (i.e. antero-septal, antero-posterior, and postero-septal).

Because the septal wall leaflet is fairly fixed, there is little room for movement if the free wall of the right ventricular/tricuspid annulus should dilate (7). Dilatation of the tricuspid annulus therefore occurs primarily in its antero-posterior (mural) aspect, which can result in significant dysfunction of the valve as a result of leaflet malcoaptation (8,9). Leaflet coaptation represents the proper joining together of the different leaflets when the valve closes. The area of the annular plane to the atrial surface of the leaflets is called the tethering area, this term is often used together with the tethering/coaptation depth which stands for the distance from the annular plane to the begin point of leaflet coaptation (10).

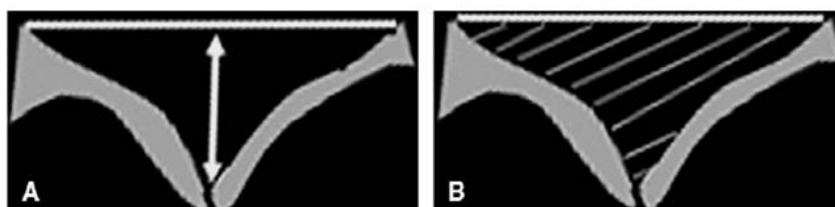


Figure 3: TV tethering/coaptation depth (A) and tethering area (B) (10).

The tricuspid annulus has a complex 3-dimensional structure, which differs from the more symmetric “saddle-shaped” mitral annulus. Healthy subjects normally have a nonplanar, elliptical-shaped tricuspid annulus, with the postero-septal portion being “lowest” and the antero-septal portion the “highest” (Figure 4). Patients with functional TR (see next paragraph) generally have a more planar annulus, which has dilated primarily in the antero-posterior direction, resulting in a more circular shape as compared with the elliptical shape in healthy subjects.

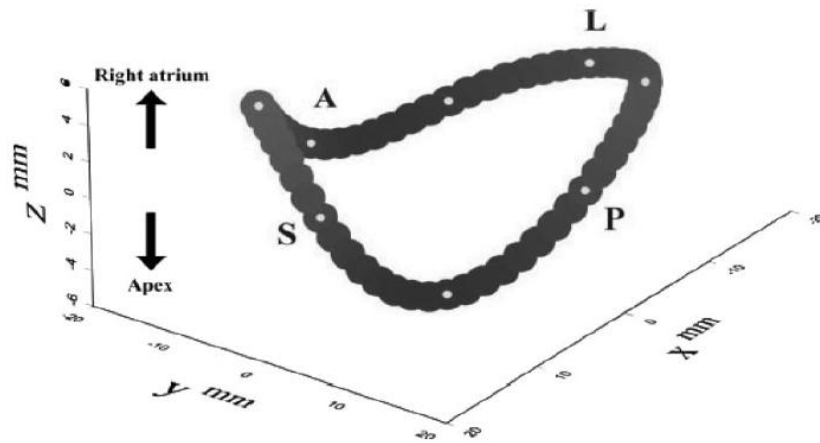


Figure 4: Three-dimensional shape of the tricuspid annulus. Reconstructed representation of the tricuspid annulus based on a 3-dimensional transthoracic echocardiographic study in healthy subjects. Note that the annulus is not planar and that an optimally shaped annuloplasty ring may need to mimic this configuration. A, indicates anterior; L, lateral; P, posterior; S, septal (11).

## 1.2 Tricuspid valve regurgitation

Tricuspid valve regurgitation (TR) or insufficiency is a disorder which implies a backflow of blood from the right ventricle to the right atrium during contraction of the right ventricle (Figure 5). TR is a common echocardiographic finding that is present in 80 to 90% of normal individuals (3). The cause of TR is more often functional (secondary) rather than morphological (primary).

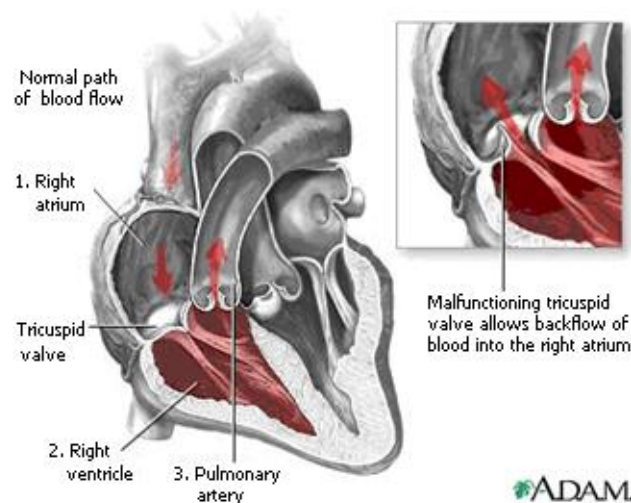


Figure 5: Normal right-sided blood flow. Flow pattern: 1. Right atrium, 2. Right ventricle, 3. Pulmonary artery. Input: Tricuspid regurgitation, with backflow of blood in the right atrium (12).

In morphological TR, as the name already predicts, the leaflets themselves are morphologically affected which results in a dysfunctional tricuspid valve (13). Congenital defects, trauma, carcinoid heart disease, toxic effects of chemicals, tumors, myxomatous degeneration, rheumatism or endocarditis, possibly together with rupture of chordae or papillary muscles are the main causes of morphological TR.

Functional TR is often called secondary TR because it results most commonly from a left-sided heart disease, right ventricular volume and pressure overload (9,14,15). Functional or secondary tricuspid regurgitation can be defined as the incompetence of the TV in the absence of any structural leaflet disease (11). This incomplete leaflet closure is thought to be caused by the dilatation of the tricuspid annulus (TA) and tethering of the tricuspid leaflet, subsequent to right ventricular dilatation and dysfunction which is associated with papillary muscle displacement (16,17).

Functional TR is often unrecognized, being only apparent during periods of increased preload and afterload. Therefore are the preload, the afterload and the right ventricular (systolic) function in addition to tricuspid dilatation very important deterministic factors of TR. This may explain why TR is difficult to accurately assess because these factors can interfere with regard to the severity of TR under different conditions. The preload can be seen as the end-diastolic volume, associated with the ability of ventricular filling, during relaxation of the heart (diastole). The afterload corresponds with the force against which the ventricle must eject its contents during contraction of the heart (systole). The right ventricle's afterload depends (partly) on the mean pulmonary arterial pressure.

Generally, the symptoms of the left-sided heart disease predominate in those patients with secondary tricuspid valve disease. With primary TR, or secondary TR being in an advanced stage, patients may experience fatigue and decreased exercise tolerance as a result of decreased cardiac output. They may also experience the classic symptoms of "right-sided heart failure" from elevated right atrial pressures such as ascites, congestive hepatopathy, peripheral edema and dyspepsia.

Clinically, and in the literature, tricuspid valve disorders receive less attention as compared to the primary left-sided disease. It is frequently labeled as "the forgotten valve" since surgical correction is still often ignored. Appropriate treatment of the tricuspid valve disease, even when secondary to left heart diseases, may improve long-term functional outcome.

### **1.3 Strategies for tricuspid valve surgery**

Consecutive observations that mitral valve surgery sometimes lead to an improvement in functional tricuspid regurgitation resulted in recommendations in the late 1960s for a conservative approach to functional tricuspid insufficiency (18). But, since positive TA remodelling is not routine after MV surgery and most patients increase their TR degree years after surgery, a new era of aggressive intervention on the tricuspid valve has heralded by the early 1980s (19,20). Additionally, concomitant surgical repair of TR at the time of mitral valve surgery should even be considered standard of care as this approach has been shown to result in improved perioperative outcomes, functional class and survival (21-24). Although, the current surgical volume of tricuspid valve repair (and replacement) as quantified in the Society of Thoracic Surgeons National Cardiac Database represents only approximately one-tenth of the >40 000 mitral valve operations performed yearly in the United States (25).

Organic TV disease, which is associated with morphological TR, often requires TV replacement surgery but the procedure is rare and is associated with significant mortality and morbidity (26). Surgical repair of the tricuspid valve is the preferred surgical strategy for functional TR but may need to be tailored to the stage of the disease, guided by underlying etiology and pathology.

The main surgical approach to repair functional TR is tricuspid annuloplasty (TVP), which involves rigid and flexible annular bands that are used to reduce annular size and achieve leaflet coaptation. Another approach includes the De Vega non-ring annuloplasty, also called the partial purse-string suture technique, to reduce the anterior and posterior portions of the annulus but recurrent TR after surgery is more common (Figure 6). The ideal TV annuloplasty would resolve the incomplete TV coaptation instigated by both TA dilatation and leaflet tethering, but sometimes these modalities are not sufficient to correct a highly tethered TV. Leaflet augmentation can resolve this problem, nevertheless, it is time-consuming and not suitable for all patients, because of another valvular involvement or the procedure is already a redo which carries higher mortality rates (27).

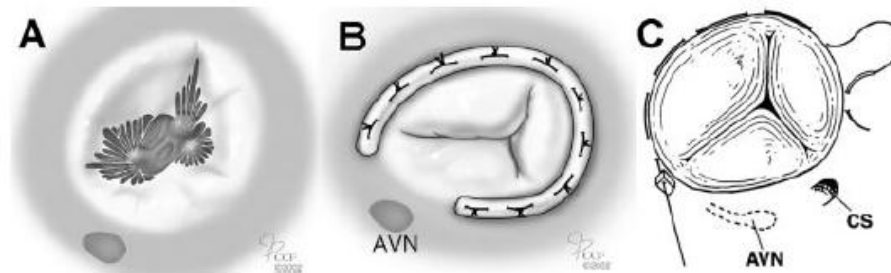


Figure 6: Predominant surgical repair techniques for functional tricuspid regurgitation. The main surgical approaches for correcting functional TR in the presence of a dilated annulus are shown. A: Dilated tricuspid annulus with abnormal circular shape, failure of leaflet coaptation, and resultant TR. B: TVP is used to restore a more normal annular size and shape. The open ring spares the atrioventricular node (AVN), thus reducing the incidence of heart block. C: De Vega-style suture annuloplasty in which a purse-string suture technique is used to partially plicate the annulus and reduce annular circumference and diameter. Coronary sinus = CS (15).

Criteria and optimal strategy for treatment of functional TR at the time of a concomitant left-sided heart-valve surgery still remain controversial nowadays. It is well recognized that patients with severe functional TR should have concomitant tricuspid valve repair, but the management of mild or moderate TR at the time of left-sided heart-valve surgery continues to be debated. However, the presence of mild TR alone should not be a criterion to indicate the need for concomitant tricuspid valve repair at the time of left-sided heart-valve surgery. Recent evidence even supports intervention on the tricuspid valve in less than mild TR during concomitant left-sided heart valve surgery if associated with tricuspid annular dilatation (21). This increasing acceptance is reflected nowadays by the endorsement of TVP to be performed during left-sided surgery in case of TA dilatation ( $>40$  mm or  $21$  mm/m<sup>2</sup>) or functional TR by the Guidelines from the European Society of Cardiology (ESC), American Heart Association (AHA) and American College of Cardiology (ACC) (28,29).

However, this recommendation has been derived from studies evaluating the effect of TVP in a very selected population undergoing mitral valve repair alone. Whether these results can be extrapolated to patients scheduled for mitral valve annuloplasty (MVP) or replacement (MVR) in addition to complex left-sided heart surgery is unknown. Additionally, the widely adopted surgical risk model as the EuroSCORE®, does not take TVP into account, and may therefore not accurately predict outcomes in patients undergoing TVP. Currently, no data of preoperative predictors for adverse events in this patient population exist.

While the effect of mitral valve surgery on LV shape and function in patients with severe functional mitral regurgitation (MR) or in patients with MR due to degenerative valve disease (30-36) has been extensively studied, similar studies evaluating changes in RV function and geometry in response to TVP are surprisingly scarce. Although results have shown that mitral valve repair

induces reverse LV remodeling in a gradual and time-dependent fashion, more information is needed to determine whether TVP has similar beneficial effects on RV shape and function. Preliminary observational data have recently shown that at 2-year follow-up, TVP may prevent adverse RV remodeling or increased TR in patients with TA dilatation undergoing mitral valve repair (37). However, it is uncertain whether these findings can be extended to patients with TA dilatation scheduled for left-sided heart surgery other than mitral valve repair alone, and whether the effect of TVP on RV mechanics is different for patients with TA dilatation compared to those undergoing TVP because of severe coexistent TR.

Therefore, the objectives of this study are, first, to compare clinical outcomes of patients undergoing mitral valve surgery during complex left-sided heart surgery either with or without TVP (in case of annulus dilatation or functional TR). Second, we sought to evaluate the prognostic value of both preoperative echocardiographic parameters and the EuroSCORE® in our particular population. Third, to compare the differential effects of TVP performed because of TA dilatation or significant functional TR on RV function, geometry and size in patients scheduled for complex left-sided heart surgery.

Since guidelines concerning TVP are based on results in patient populations who underwent TVP in association with MVP without complex left-sided heart surgery we hypothesize that more adverse events are expected in our study population, associated with a worse prognostic value of the EuroSCORE® together with several predictive echocardiographic parameters. This in conjunction with short-term reverse RV remodeling but associated with systolic function deterioration after TVP, based on previous findings about LV reverse remodeling and function after MVP, being more pronounced in patients undergoing TVP because of severe coexisting TR.

Additionally, we try to indicate which patients benefit the most after TVP surgery with a reduction in discomfort and symptoms, leading to a better quality of life. All together, this will contribute to a decrease in the health care costs and the total number of hospitalizations.





## **2. General Materials and Methods**

### **2.1 Setting up the database**

To construct a consistent database, the appropriate information was filtered out of large databases in a retrospective way. The standard program to store all information about patients involved with cardiology is called 'Medar', an electronic health record. After scanning their identification and insurance card at the check-in desk, every patient gets its unique ID number inside the hospital's server. Only doctors, surgeons or other employees who are authorized (to), can add or delete information from a patient's file in 'Medar'. The rest of the medical staff also has access to this information but are only authorized to read the patient's information. 'MediWeb Resultserver' is the program which joins all data from the hospital's different departments together to have access to all information related to a specific patient.

Patients who were scheduled for mitral valve surgery (MVP or MVR) and/or TVP were selected out of the surgeons' database, called 'Patient files heart surgery'. Possibly, aortic valve surgery and/or coronary artery bypass grafting (CABG) was concomitantly performed with the mitral and/or tricuspid valve surgery since some patients had severe heart problems. Nearly all patients had MR and TVP was routinely performed in case of TA dilatation (echocardiographic: greater than 40 mm or 21 mm/m<sup>2</sup> apical 4-chamber view end-diastolic) and/or more than moderate (TR>2) functional TR (38). General data about all of these patients was gathered out of 'Medar' and 'MediWeb Resultserver'. The gathered information included sex, date of birth, date of surgery, risk factors associated with heart problems, cycloergspirometry results, lung function results, blood results, medication use before and after the surgery, date of death and rehospitalization due to HF. Information about the surgery itself was collected as well. These parameters included cross clamp time, cardiopulmonary bypass time (CPB), repair/replacement ring size (MV and/or TV ring), repair/replacement ring type, type of cardioplegia, length of stay on intensive care.

Short echo reports were added to medar by cardiologist after each consult, the full reports and images were stored in another database, which could be visualized by the program 'Xcelera Echo' (Philips medical systems, Eindhoven, version 1.2). This program was used to analyze echo data by looking up the moving echo images and echo reports. A two week training at echocardiography gave me much insight in the techniques and equipments, but proper technical and cognitive skills are required for optimal application of echocardiography and the interpretation of its results. Thereby, a sonographer had to supervise me during the measurements or did measurements herself in some cases when the images were of bad quality.

This thesis is based on two articles I wrote with intensive support of the cardiovascular department of the Hospital Oost Limburg. Since both articles have different patient populations and different data analyzed, I subdivided the rest of my thesis in accordance with the articles to have a clearer overview (Article: Clinical outcomes ; Article: RV function and geometry). Although, I made a general conclusion.

### **3. Article: Clinical outcomes**

#### **3.1 Materials and methods**

##### ***3.1.1 Study population***

All consecutive patients who underwent MVP/MVR only or in addition to CABG and/or aortic valve surgery between 2007-2010 in the Hospital Oost Limburg with subsequent clinical follow-up in our center were reviewed for this study. All patients had severe MV regurgitation and TVP was routinely performed in case of TA dilatation (>40 mm apical 4-ch view end-diastolic) and/or more than moderate functional TR (21). The study complies with the Declaration of Helsinki, the locally appointed ethics committee has approved the research protocol, and informed consent for prospective follow-up has been obtained from all subjects.

##### ***3.1.2 Surgical procedure***

All surgical procedures were performed through midline sternotomy under normothermic cardiopulmonary bypass with intermittent antegrade warm-blood cardioplegia. Patients with an indication for revascularization underwent first CABG. The mitral valve was exposed through a vertical transeptal approach along the right border of the foramen ovale, leaving the left atrial roof untouched. MVP was performed after thorough intra-operative visual and echocardiographical valve analysis. Ring size (Carpentier-Edwards Physioring®, Edwards Lifesciences, Irving, CA) was determined after careful measurement of the height of the anterior leaflet. In case of functional MR, downsizing by two sizes (ie, size 26 when measuring 30) was applied to ensure a coaptation length of at least 8 mm. Rings were inserted using 12 to 14 deep U-shaped simple horizontal sutures using Ethibond 2-0 (Ethicon®, Inc, Somerville, NJ). Additional aortic prosthetic valve replacement (AVR) or aortic valve repair (AVP) was performed in patients with aortic lesions, if indicated. Additional TVP was performed in patients with TR exceeding grade 2 on a preoperative transthoracic echocardiogram or patients with a dilated tricuspid annulus exceeding 40 mm on a transesophageal echocardiogram in the operating room. TVP was performed using a Carpentier-Edwards MC3® ring. The ring size was visually matched to the area of the anterior leaflet. More recently, in presence of a markedly dilated RV resulting in non-coaptation of the leaflet, the anterior leaflet was widely augmented using an autologous pericardial patch (27).

The restored leaflet coaptation ( $\geq 8$  mm for mitral valve) was confirmed at the time by filling the ventricles with saline through a bulb syringe and visually inspecting the leaflets. This, in conjunction with intra-operative transesophageal echocardiography to assess LV and valve function after weaning from CPB. If these criteria were not met, further downsizing was performed.

### ***3.1.3 Transthoracic echocardiography***

Comprehensive two-dimensional echocardiographic exams were performed with a commercially available system (Philips Medical Systems, IE33®) by experienced Diagnostic Cardiac Sonographers. Images were acquired in the left lateral decubitus position and standard two-dimensional and Doppler data, triggered to the QRS complex, were digitally stored in cine loops in DICOM format.

The analysis was performed offline by two independent investigators experienced with echocardiographic measurements, blinded to surgical or clinical data at the time of analysis. All reported echocardiographic measurements were averaged from three consecutive cycles and assessed as recommended by the American Society of Echocardiography (39).

From the parasternal view, the left ventricular diameters were measured. The left ventricular ejection fraction (LVEF) was obtained by using Simpson's rule methods from apical 4- and 2-chamber views (40). The RV end-systolic and end-diastolic areas were measured by planimetry. Right ventricular fractional area change (RVFAC) was used to determine the RV systolic function and was calculated by the following formula:  $FAC = [(diastolic\ area - systolic\ area) / diastolic\ area] \times 100\%$  (38). RV long-axis length and RV short-axis width were measured at the mid-ventricular level and used to calculate the right ventricular sphericity index (RVSI) at end-systole (40). TV annulus diameter was measured at end-systole and end-diastole as the distance between the midpoints of reflection of the septal and mural endocardium on the anterior and septal tricuspid leaflets, respectively (41). MR and TR severity were assessed by color Doppler flow mapping (3).

### ***3.1.4 Endpoints***

The duration of follow-up was defined as the interval from the surgery to all-cause mortality, first HF hospitalization or May 1, 2011. All-cause mortality was analyzed using data documented in the electronic health record. A secondary endpoint was days to first HF hospitalization, defined as an admission of more than 12 hours for worsening HF symptoms requiring parenteral therapy (at our center or at any other facility reported in the medical record). Thirty-day in hospital mortality was also predicted by calculating the EuroSCORE® for each patient.

### ***3.1.5 Statistical analysis***

All the results are expressed as mean  $\pm$  standard deviation or as percentages. The categorical and continuous demographical variables were compared using the chi-square test and two-paired Student t-test, respectively. Statistical significance was set at a 2-tailed probability level with  $\alpha=0.05$ . Kaplan-Meier survival curves were calculated with the combined endpoints for all patients stratified in two groups. The Cox proportional hazards regression model was used to determine the prognostic value of both clinical and echocardiographic parameters. Variable selection in multivariate analysis was based on the clinical and statistical significance of the

univariate analysis. The authors had full access to the data and take responsibility for its integrity. All statistical analyses were performed using SPSS for Windows, release 17.0 (SPSS Inc., Chicago, Illinois). All authors have read and agreed to the manuscript as written.

## **3.2 Results**

### ***3.2.1 Patient characteristics***

Of the total of 196 consecutive patients undergoing MVP/MVR, 6 were excluded because of suboptimal baseline echocardiographic image quality and 15 because of missing follow-up data. The final population of this study comprised 175 patients (88 men and 87 women; 15% MVR and 85% MVP), which were divided in two groups. The TVP- group consisted of 86 patients who underwent complex left-sided heart surgery without concomitant TVP (46 men, 40 women,  $69 \pm 12$  years), in contrast to 89 TVP+ patients who underwent TVP concomitant with complex left-sided heart surgery (42 men, 47 women,  $68 \pm 11$  years). The preoperative patient demographics are listed in Table 1. Baseline characteristics including LVEF, MR gradation and RVSI were similar among both groups. However, the TVP+ had less ischemic but more Barlow and non-ischemic etiology of their MR, a lower RVFAC, higher baseline TR grade and more TA dilatation compared with the TVP- patients. All patients received optimized medical therapy as advocated per guidelines (Supplemental Results, Table 1).

### ***3.2.2 Surgical details***

All patients underwent successful MVP/MVR and TVP defined as no residual mitral/tricuspid regurgitation and an immediately postoperative coaptation length of the valve leaflets of  $\geq 8$  mm. The mean mitral ring size used was  $31.4 \pm 4.1$  mm and the mean tricuspid ring size used was  $31.2 \pm 2.4$  mm. Patients in the TVP- group had more concomitant CABG performed but less aortic valve surgery compared with patients in the TVP+ group (Table 2). 30% of the TVPs were performed because of moderate or severe preoperative functional tricuspid insufficiency and 70% because of TA dilatation in absence of significant ( $>2$ ) TR. CPB time and cross clamp time were comparable between the groups;  $206.7 \pm 75.6$  vs.  $201.5 \pm 57.7$  minutes and  $150.6 \pm 56.5$  vs.  $151.6 \pm 48.9$  minutes, respectively (Table 2).

**Table 1: Baseline characteristics**

	TVP-	TVP+	p-value
n	86	89	
Age (yr)	68±11	69±12	0.6
Sex, female	46.5%	52.8%	0.405
Diabetes	17.9%	15.7%	0.735
Arterial hypertension	43.3%	57.8%	0.081
Obesity	20.8%	9.2%	<b>0.049</b>
Smokers	22.4%	13.2%	0.147
Hypercholesterolemia	41.8%	40.8%	0.9
Familial predisposition	32.8%	27.6%	0.498
Creatinine	1.2 ± 1.7	1.1 ± 0.3	0.126
LVEF (%)	57.9 ± 13.5	53.8 ± 15.6	0.066
MR grade	2.7 ± 0.9	3 ± 1	0.12
TR grade	0.6 ± 0,6	1.8 ± 1	<b>&lt;0.001</b>
TA diameter (cm)	3.0 ± 0.47	3.7 ± 0.61	<b>&lt;0.001</b>
RVFAC (cm)	0.4 ± 0.1	0.3 ± 0.1	<b>0.013</b>
RVSI (cm)	3 ± 0.8	2.8 ± 0.9	0.12
<b>MV pathology</b>			
Degenerative	30.2%	27%	0.633
-Barlow	1.2%	9%	<b>0.019</b>
-Fibro-elastic deficiency	29%	18%	0.083
Rheumatic	19.8%	21.3%	0.94
Endocarditis	8.1%	2.3%	0.078
Functional	41.9%	46.1%	0.57
-Ischemic	33.7%	15.8%	<b>0.006</b>
-Non-ischemic	8.2%	30.3%	<b>&lt;0.001</b>
Others*	0%	3.3%	0.087

LVEF= left ventricular ejection fraction; MR= mitral regurgitation; TR= tricuspid regurgitation; TA= tricuspid annulus; RVFAC= right ventricular fractional area change; RVSI= right ventricular sphericity index;

\*Other pathologies included: paravalvular leakage and myocarditis.

### **3.2.3 Follow-up**

Thirty-day mortality was higher in the TVP+ group compared to the TVP- group (13.5% vs. 4.7%, p=0.042) (Figure 7). While the mean predicted EuroSCORE® in the TVP- group was much higher than the actual thirty-day mortality (predicted 9.8% vs. actual 4.7%), the TVP+ group's predicted EuroSCORE® was similar to the actual thirty-day mortality (predicted 14.2% vs. actual 13.5%). Patients were followed over a maximum time period of 2.5 years, with a mean follow-up time of 15 months. Follow-up duration was similar for both groups (16.2 ± 10.6 months in the TVP- group and 14.8 ± 11.5 months in the TVP+ group, p=0.429). Mean TR grade at 1 year follow-up was 0.67 ± 0.64 and 0.57 ± 0.69, respectively in the TVP- and TVP+ group.

A total of 25 patients (10 TVP- patients and 15 TVP+ patients) died, and 37 patients (13 TVP- patients and 24 TVP+ patients) developed HF during a mean follow-up period of 15 months. The actuarial survival during follow-up was 88.4% in the TVP- group and 83.2% in the TVP+ group (Figure 8,  $p=0.321$ ). Freedom of hospital admission due to HF was 83.3% in the TVP- group and 68.8% in the TVP+ group (Figure 9,  $p=0.045$ ). Combined clinical outcomes resulted in an event-free survival of 75.6% in the TVP- group and 59.5% in the TVP+ group (Figure 10,  $p=0.025$ ). TVP itself was the only predictor for adverse events in a multivariable analysis including LVEF, age, RV function and geometry ( $p=0.04$ , HR: 1.8; 95% CI 1.1-3.1).

Subanalysis of patients undergoing MVP only vs. MVP/TVP only revealed similar 30-day mortality and mid-term mortality but more frequent HF admissions in the group undergoing TVP.

**Table 2: Perioperative characteristics**

	TVP-	TVP+	p-value
n	86	89	
Left-sided procedures			
MVP/MVR	38.3%	51.6%	0.078
MVP/MVR + CABG	48.9%	21.4%	<b>&lt;0.001</b>
MVP/MVR + AVR/AVP	4.7%	19.1%	<b>0.003</b>
MVP/MVR + CABG + AVR/AVP	8.1%	7.9%	0.947
EuroSCORE			
	9.8%	14.2%	0.063
Cross clamp time (min)	150.6 ± 56.5	151.6 ± 48.9	0.904
CPB (min)	206.7 ± 75.6	201.5 ± 57.7	0.623

MVP= mitral valve annuloplasty; MVR= mitral valve replacement; CABG= coronary artery bypass grafting; AVR= aortic valve replacement; AVP= aortic valve repair; CPB= cardiopulmonary bypass.

### **3.2.4 Echocardiographic predictors of clinical outcome**

Only RVSI, surrogate for RV volume overload was significantly related to adverse outcomes in multivariable analysis including LVEF, age, RV function and tricuspid regurgitation ( $p=0.02$ , HR: 1.4; 95% CI 1.1-1.8). No other preoperative echocardiographic finding was predictive for adverse events.



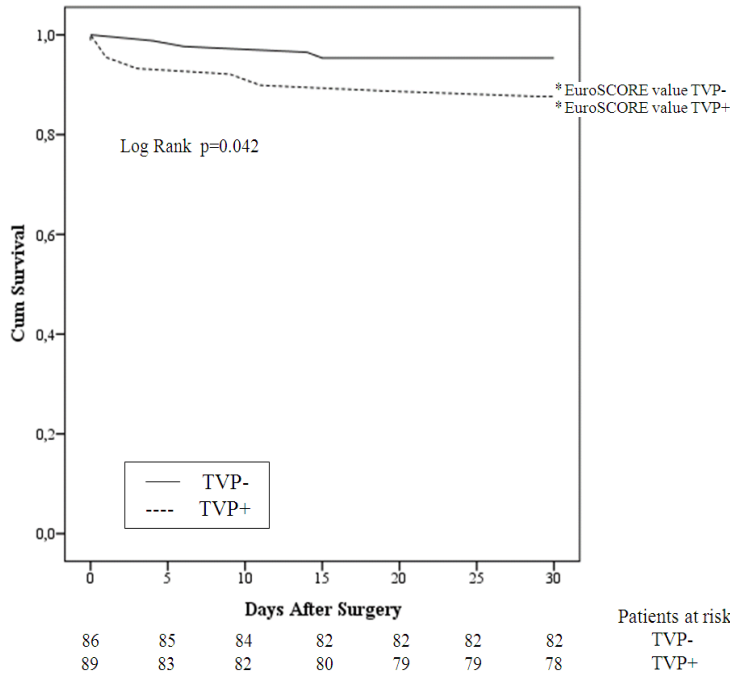


Figure 7: Kaplan-Meier curves comparing 30-day mortality between TVP- (—) and TVP+ (---). With \* indicating the predicted EuroSCORE® within each group.

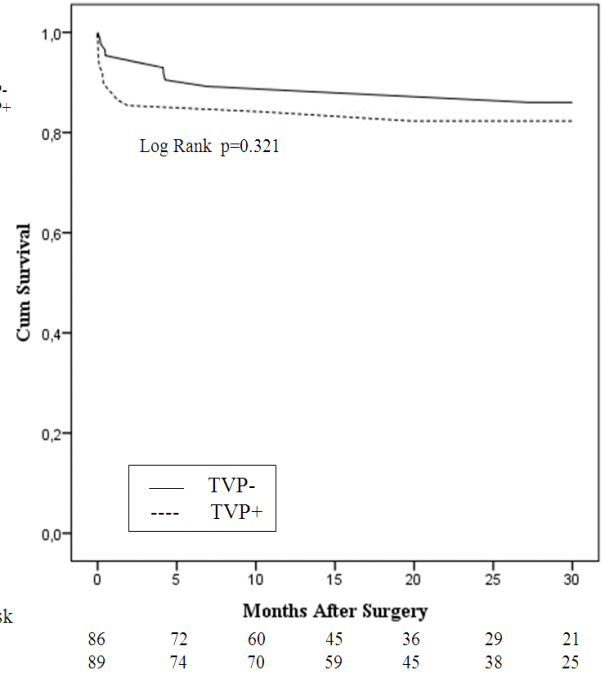


Figure 8: Kaplan-Meier curves, comparing cumulative survival between TVP- (—) and TVP+ (---).

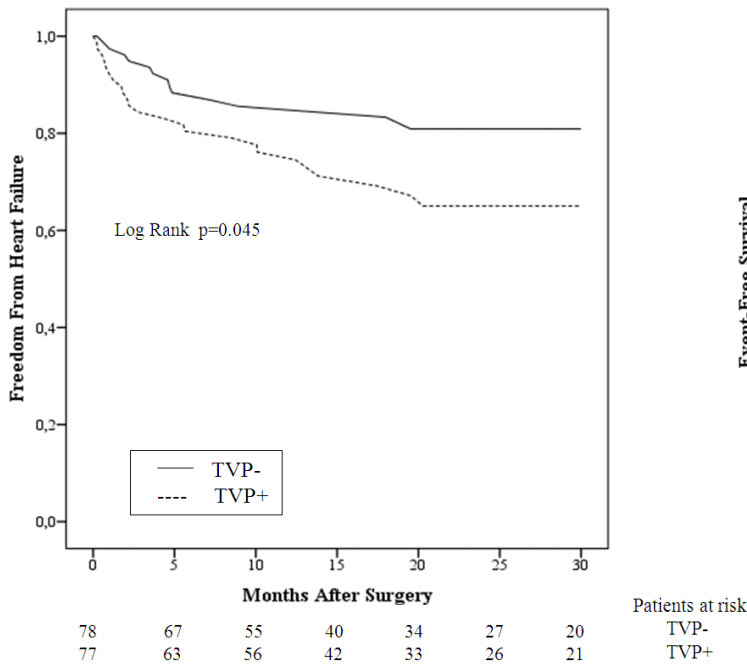


Figure 9: Kaplan-Meier curves, comparing freedom from heart failure between TVP- (—) and TVP+(---).

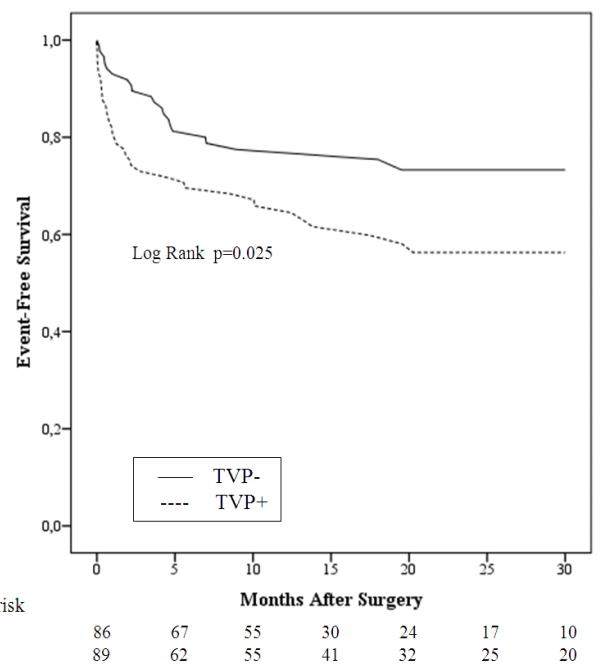


Figure 10: Kaplan-Meier curves, comparing event-free survival between TVP- (—) and TVP+ (---).

### **3.3 Discussion**

From our large consecutive contemporary cohort of surgical patients undergoing MVP/MVR during complex left-sided surgery who have been treated in an experienced tertiary referral center, we report for the first time clinical outcome data related to the addition of TVP in case of moderate functional TR or TA dilatation. In comparison with standard MVP/MVR, the addition of TVP is associated with an increased risk of adverse events, even in experienced hands and independent of most preoperative echocardiographic findings. Importantly, most adverse events are related to HF hospitalizations, mostly overlooked in classical post surgical outcome data. Additionally, while the most widely used cardiac surgical risk model (i.e. EuroSCORE®) overestimates the actual survival curve for patients undergoing MVP/MVR, EuroSCORE® accurately predicts outcomes when TVP is added during MVP/MVR. With increasing application of TVP concomitant with MVP, even in the cardiac society guidelines, to prevent further TR in case of functional TR or TA dilatation, our observations provide an important refinement in the clinical interpretation of this approach as it might be associated with more adverse events, especially with regards to HF hospitalizations in higher risk groups.

Our patient cohort with advanced left-sided heart disease amendable for cardiac surgery was derived from a tertiary heart care referral center being treated with contemporary guideline-based medical and interventional therapies. The cardiac surgical team has a vast experience in heart valve surgery, operative 30-day mortality is excellent and well below the predicted mortality by the EuroSCORE® in the TVP- group and just below the predicted mortality by the EuroSCORE® in the TVP+ group. Long-term results of the TVP were excellent with most patients having less than 1+ TR after one year.

Functional TR is the most common type of tricuspid valve pathology occurring mostly from annular dilatation and usually found in the setting of left-sided valvular disease, right ventricular volume and pressure overload (15). Historically, it was thought that MVP/MVR would diminish or decrease functional TR (18). However, increasing evidence has shown that functional TR does not always disappear but can progress or appear de novo if the tricuspid valve is untreated at time of left-sided surgery (42-44). Additionally, significant progression of TR in patients having moderate or less TR undergoing MVP/MVR will occur in up to 25% of the cases at 1 year, up to 53% at 3 years and more than 74% late during follow-up (45). Therefore, the traditional view that functional TR or TA dilatation diminishes with surgical correction of the primary left-sided lesions is no longer accepted (19). This increasing acceptance is reflected by the endorsement of TVP to be performed during left-sided surgery in case of TA dilatation or functional TR by the Guidelines from the European Society of Cardiology, American Heart Association and American College of Cardiology (28,29). However, though progression of TR might be prevalent after

MVP/MVR, safety of the addition of the procedure has not been studied. While we could not corroborate progression of TR after left-sided surgery in case of preexisting functional TR, data reported in this manuscript/thesis are unique in several ways. Firstly, we were one of the first centers to judiciously adopt these guidelines into daily clinical practice. All patients scheduled for left-sided surgery only (without TVP) had no or at most mild TR preoperatively. Secondly, comparison of clinical outcomes including HF events between patients undergoing complex left-sided heart surgery including MVP/MVR with or without TVP (in case of mild TR/annulus dilatation) was possible due to the strict follow-up of our patients. Therefore, the challenge to better identify those patients who would benefit most from such a procedure might be investigated.

In the present study, no clear early or continuous significant separation of the mortality curves for the two cohorts was found. While the initial 30-day mortality was significantly higher for patients undergoing TVP, this probably was related to differences in patient profiles. Indeed, once the immediate postoperative period has passed, survival was excellent.

While Dreyfus et al. (21) have described better mid-term survival of patients undergoing TVP at time of MVP, differences in patient profiles with our patients clearly being sicker (lower LVEF), older and undergoing more complex left-sided surgeries might account for that. Additionally, though no significant differences were found regarding 30-day in-hospital mortality and mid-term survival, HF episodes were not reported in the Dreyfus' study (21). Nevertheless, subanalysis of a subset of patients undergoing only MVP with/without TVP in our population did corroborate similar 30-day mortality and mid-term mortality, but still demonstrated significantly more HF events when additional TVP was performed.

Though patient groups in our study were not completely comparable as reflected by higher EuroSCORE®, more concomitant aortic valve surgeries, more non-ischemic and Barlow disease as reason for MR, and the presence of TR/TA dilatation in the TVP+ group, our study provides an important rationale for *no* routine addition of TVP in this patient population, as there was an increased adverse event rate, mostly related to HF hospitalizations after surgery. Importantly, the early and continuous separation of the hospitalization curves for the two cohorts implies a continued and increasing risk of patients after TVP for HF hospitalizations throughout the follow-up period. The fact that this was observed in patients independently of their baseline LV function or treatment with neurohormonal blockers, lends credence to the suggestion that TVP (or the preceding functional TR/TA dilatation) might exert a negative effect via mechanisms independent of baseline LV function or treatment. Importantly, since there was no recurrent TR at 1 year follow-up implicates that the surgical strategy to eliminate or prevent TR recurrence/evolution

was successfully completed, and that recurrence of functional TR itself had no role of importance with respect to the adverse events. Since clamping times were also similar, exposure time of the RV to ischemia could also not be held responsible for the observed outcomes.

Therefore, one might wonder whether the higher adverse event rate in the TVP+ group might be contributed to a negative response of the right ventricle to the annuloplasty procedure (or preceding functional TR/TA dilatation) by mechanisms which are yet unknown, and from which it might never recover completely. A significant difference in baseline RVFAC existed in TVP+ patients suggesting more extensive RV remodeling. This finding might indicate that the underlying intrinsic cardiac disease remains an important determinant of the “reserve” available for the (right) heart after relief of ‘the escape route of the TR’ and to respond to the challenge posed by the ischemia during complex left-sided cardiac surgery. Our previous findings of higher long-term adverse events if RV mechanics fail to improve in response to intensive medical therapy in patients with advanced decompensated HF lends credence to this hypothesis (46). However, in contrast with medical therapy, TVP may result in anatomical reverse remodeling of the RV but maybe without restoration of intrinsic RV systolic function in a significant part of the population when mild pre-existing RV dysfunction is present (more information about this concept is available in the other, next, article). Naturally, this finding raises the question as to whether treatment primarily directed with the aim of “prevention of TR” should be administered routinely (i.e. in patients without severe TR), especially in this extraordinary high-risk group.



## **4. Article: RV function and geometry**

### **4.1 Materials and methods**

#### ***4.1.1 Study population***

The patient population consisted of 49 consecutive patients that underwent TVP between 2007-2010 at the Hospital Oost Limburg, usually as part of complex left-sided heart surgery (Table 3). The decision to perform TVP in these patients was made by the cardiac surgeon based on the presence of more than moderate TR and/or TA dilatation defined as a TA diameter exceeding 40 mm or 21 mm/m<sup>2</sup> on preoperative echocardiography as proposed recently (21). Patients with structural (organic) tricuspid valve disease were excluded from our study. One patient with history of left-sided surgery undergoing isolated TVP as a redo procedure was also included. Only patients with preoperative and postoperative echocardiographical studies performed at our center were included in the analysis. This retrospective study was approved by the locally appointed ethics committee which waived the need for individual consent.

#### ***4.1.2 Surgical procedure***

All surgical procedures were performed through midline sternotomy under normothermic cardiopulmonary bypass with antegrade warm-blood cardioplegia. Every 15 minutes, cross clamping was interrupted to perform a 3 minute cardioplegia. Patients with an indication for revascularization underwent CABG. First, if necessary, the MV was exposed through a vertical transeptal approach along the right border of the foramen ovale, leaving the left atrial roof untouched. In patients with structural MV disease, MVP was performed after thorough intraoperative visual and echocardiographical valve analysis according to standard Carpentier techniques (47). In patients where the MV was deemed irreparable, mitral valve replacement (MVR) was performed. Mitral annuloplasty ring size (Carpentier-Edwards Physioring®, Edwards Lifesciences, Irving, CA) was determined after careful measurement of the height of the anterior leaflet; in patients with functional mitral regurgitation, downsizing by two sizes (i.e., size 26 when measuring 30) was routinely performed. In patients with severe degenerative aortic valve disease, AVR was performed if indicated. TVP was performed with a Carpentier-Edwards Classic® or MC3® ring (both manufactured by Edwards Lifesciences) with downsizing by 1 size using the surface of the anterior leaflet as a reference. In patients with severe TV leaflet tethering, an additional pericardial patch augmentation of the anterior leaflet was performed to increase tricuspid leaflet coaptation (27). The restored leaflet coaptation was confirmed at the time of surgery by filling the RV/LV with saline through a bulb syringe and by visually inspecting the leaflets. Additionally, after weaning from cardiopulmonary bypass, intraoperative transesophageal echocardiography (TEE) was used to assess the result of valve reconstructions.

### **4.1.3 Transthoracic echocardiography**

Comprehensive two-dimensional (2D) echocardiographic exams were performed with a commercially available system (Philips Medical Systems, IE33®). Standard 2D and Doppler echocardiography images were acquired in the left lateral decubitus position using a phased-array transducer in the parasternal and apical views by experienced sonographers. Three consecutive cardiac cycles were recorded and stored for subsequent offline analysis. LV end-diastolic and end-systolic dimensions were measured from parasternal M-mode acquisitions. LV volumes and ejection fraction were calculated using Simpson's biplane method according to the guidelines of the American Society of Echocardiography (39). Left and right atrial areas were measured by planimetry at end-systole from the apical 4-chamber views. Left atrial volumes were measured by the biplane Simpson's method. Color flow was applied in the apical 4-chamber view to assess the severity of MR and TR which was graded semi-quantitatively on a scale from 0 to 4 as follows: 0; none or trace, 1; jet area/left atrial area <10%, 2; jet area/left atrial area 10%-20%, 3; jet area/left atrial area 20%-33% and 4; jet area/left atrial area >33%) (48). The transtricuspid gradient was measured using the modified Bernoulli equation (continuous-wave Doppler scanning).

From the apical 4-chamber view, the RV end-systolic and end-diastolic areas were measured by planimetry with the transducer positioned to maximize the RV area and to include the RV apex. RVFAC was used to determine the RV systolic function and was calculated by the following formula:  $FAC = [(diastolic\ area - systolic\ area)/diastolic\ area] \times 100\%$  (38). RV long-axis length and RV short-axis width at the mid-ventricular level were measured, and used to calculate the end-diastolic RV sphericity index as previously described ( $RVSI = RV\ long-axis\ length / RV\ short-axis\ width$ ) (40).

### **4.1.4 Statistical analysis**

All the results are expressed as mean  $\pm$  standard deviation or as percentages. The continuous echocardiographical variables were compared using the two-tailed paired Student t-test. Associations between continuous variables were explored by linear regression analysis. Logistic regression analysis and receiver operating characteristic curves (ROC) were used to define determinants and possible cutoff values predictive of postoperative RV systolic function in our patient population. Inter- and intraobserver agreement was tested by Bland-Altman analysis. Statistical significance was set at a two-tailed probability of  $p < 0.05$ . The authors had full access to the data and take responsibility for its integrity. Statistical analyses were performed using SPSS for Windows, release 17.0 (SPSS Inc., Chicago, Illinois, USA) and SAS for Windows, release 9.2 (SAS Institute, Inc., Cary, North Carolina, USA). MedCalc version 11.5.1.0 for Windows (MedCalc Software, Belgium) was used to calculate Bland-Altman plots. All authors have read and agreed to the manuscript as written.

## 4.2 Results

### 4.2.1 Patient characteristics

Baseline characteristics of our patient cohort are summarized in Table 3. All patients received optimized medical therapy prior to surgery as advocated per guidelines. Except for 1 patient undergoing isolated TVP, all patients had left-sided heart surgery with concomitant TVP. As shown in Table 4, mitral valve surgery was the main indication for left-sided heart surgery: 42 patients (86%) underwent MVP, 5 patients (10%) needed MVR. CABG was performed in 17 (35%) and AVR in 15 (31%) patients. Many patients (51%) underwent complex left-sided heart surgery and not just mitral valve surgery alone in addition to TVP (Table 4).

Surgical results were successful with residual mitral/tricuspid regurgitation of  $\leq 1$  in all patients as noted by intraoperative transesophageal echocardiography. The mean mitral ring size used was  $30.98 \pm 3.42$  mm and the mean tricuspid ring size used was  $30.6 \pm 2.16$  mm. Thirty-five percent of the TVP's were performed because of more than moderate ( $>2$ ) preoperative functional tricuspid insufficiency and 65% because of TA dilatation ( $\geq 40$  mm) in absence of significant ( $\leq 2$ ) TR. Pericardial patch augmentation of the anterior leaflet was performed in 2 (4%) patients. CBP and clamp time were  $201.7 \pm 66.3$  minutes and  $151.1 \pm 43.8$  minutes, respectively (Table 4).

### 4.2.2 Echocardiographic analysis

Echocardiography was performed at baseline ( $\leq 3$  months prior to operation), and at an average follow-up of  $3.5 \pm 3.3$  months. The results of the echocardiographic analysis are shown in Table 5. At follow-up, a reduction in MR was observed, accompanied by a parallel reduction in left atrial dimensions. Similarly, TR grade decreased, with a matched reduction in right atrial dimensions. Although diastolic RV size was overall unchanged at follow-up, it became clear that in the subgroup of patients with TR  $>2$ , RV end-diastolic size became significantly smaller at the follow-up (see Figure 11; RV end-diastolic area (RVEDA) decreased from  $21.6 \text{ cm}^2$  to  $19.1 \text{ cm}^2$ ;  $p=0.027$ ). In contrast, in patients with TA dilatation and no significant preoperative TR, RV end-diastolic size *increased* postoperatively from  $16.4 \text{ cm}^2$  to  $19.5 \text{ cm}^2$ ;  $p=0.027$ , see Figure 11). As such, the postoperative change in RV diastolic size was found to be significantly correlated with the baseline severity of TR, measured as the ratio of the TR jet area/right atrial area ( $r=0.5$ ,  $p=0.003$ ). TVP was associated with an important change in right ventricular geometry, as the diastolic RVSI increased from  $1.75 \pm 0.24$  to  $1.97 \pm 0.25$  ( $p<0.001$ , Figure 11). Interestingly, not only patients with significant TR at baseline showed an increase in RVSI (from  $1.61 \pm 0.25$  to  $1.96 \pm 0.28$ ,  $p<0.001$ ); also in those with TA dilatation and lesser degrees of TR the RV became less spherical (RVSI increase from  $1.83 \pm 0.2$  to  $1.98 \pm 0.23$ ,  $p=0.001$ ). However, the increase in RVSI at follow-up was significantly larger in the subgroup of patients with more than moderate TR preoperatively ( $p=0.02$ , additional analysis, data not shown).



A trend was noticed towards a mild reduction in RV contractility after surgical intervention (preoperative vs. postoperative RVFAC  $36.2 \pm 12.51\%$  to  $33.02 \pm 11.99\%$ , respectively,  $p= 0.1$ ; Table 5, Figure 11). A non-significant decrease in RVFAC was seen in the subgroup of patients with TA dilatation (RVFAC change from  $34 \pm 13\%$  to  $32.4 \pm 13\%$ ;  $p=0.55$ ) as well as in those with significant preoperative TR ( $40 \pm 11\%$  to  $34.2 \pm 9\%$ ;  $p=0.1$ ). The postoperative decrease in RVFAC was not significantly different in patients with more severe TR at baseline compared to those with TA dilatation ( $p=0.11$ , additional analysis, data not shown).

**Table 3: Baseline characteristics of the TVP study population**

n	49
Age (yr)	$70 \pm 11$
Sex, female	55.1%
Diabetes	13.6%
Arterial hypertension	56.8%
Obesity	6.8%
Smokers	11.4%
Hypercholesterolemia	36.4%
Familial predisposition	31.8%
NYHA class	$2.71 \pm 0.73$
<b>Patients with MV pathology</b>	
	n=47
Degenerative	24.5%
-Barlow	4.1%
-Fibro-elastic deficiency	20.4%
Rheumatic	24.5%
Endocarditis	2%
Functional	49%
-Ischemic	18.4%
-Non-ischemic	30.6%
<b>Medical therapy</b>	
ACEi/ARB	47.9%
BB	68.8%
Diuretics	79.2%
Spironolactone	29.2%
Statin	43.8%
Warfarin	25%
Aspirin	41.7%

NYHA= New York Heart Association; MV= mitral valve; ACEi/ARB= angiotensin converting enzyme or angiotensin receptor blocking agent therapy; BB= beta-blocking agents.

### **4.2.3 Determinants of postoperative RVFAC**

While for the entire study population RVFAC did not change significantly at short-term follow-up, substantial variance could be observed in the difference between pre- and postoperative RV systolic function for individual patients. To find possible determinants of postoperative changes in RV systolic function, the patient population was dichotomized in two groups according to presence or absence of a postoperative increase in RVFAC. Among the relevant variables evaluated by univariable logistic regression analysis, only age, use of angiotensin converting enzyme inhibitors or angiotensin receptor blocking agents (ACEi/ARB's) and pre-existent RV systolic function emerged as significant predictors (Supplemental Results, Table 2). In a multivariate analysis, only younger age and pre-existent RV systolic dysfunction were found to be predictive of a postoperative increase in RVFAC (Table 6). Using ROC analysis, the best cutoff values to predict a postoperative improvement in RV systolic function were age <72 years (sensitivity 71.4%, specificity 81%) and a preoperative RVFAC <35.76% (sensitivity 77.8%, specificity 81%).

### **4.2.4 Inter- and intraobserver variability**

Pre- and postoperative echocardiographic studies from 12 randomly selected patients were used to evaluate inter- and intraobserver variability in the measurement of RVSI and RVFAC. The results of Bland-Altman analysis are shown in Figure 1 (Supplemental Results), showing good agreement for both measurements. The mean difference in RVFAC between different observers was  $5.07 \pm 2.67\%$ ; for the same observer  $3.51 \pm 1.43\%$ . The mean difference in RVSI between different or similar observers was  $0.38 \pm 0.24$  and  $0.22 \pm 0.19$  respectively.

**Table 4: Surgical details of the TVP study population**

n	49
TVP in absence of MV surgery	
TVP only	2%
TVP + AVR	2%
TVP + mitral valve surgery ± other left-sided procedures	
MVP/MVR only	45%
MVP/MVR + CABG	22.5%
MVP/MVR + AVR	16.3%
MVP/MVR + CABG + AVR	12.2%
Cross clamp time (min)	151.1 ± 43.8
CPB (min)	201.7 ± 66.3

TVP= tricuspid valve annuloplasty; MV= mitral valve; MVP= mitral valve annuloplasty;  
MVR= mitral valve replacement; CABG= coronary artery bypass grafting;  
AVR= aortic valve replacement; CPB= cardiopulmonary bypass.

**Table 5: Results of echocardiographic analysis**

Variable	Baseline	Follow-up	p-value
LA area (cm <sup>2</sup> )	26.2 ± 7.74	22.49 ± 5.79	<b>&lt; 0.001</b>
LA volume (ml)	95.85 ± 37.81	78.7 ± 31.43	<b>0.003</b>
LV end-diastolic volume (ml)	114.98 ± 42.37	113.43 ± 48.13	0.766
LV end-systolic volume (ml)	55.91 ± 33.19	56.68 ± 36.84	0.828
LV ejection fraction (%)	53.76 ± 14.9	52.94 ± 13.23	0.617
LV end-diastolic diameter (mm)	5.05 ± 0.98	4.99 ± 0.88	0.59
LV end-systolic diameter (mm)	3.84 ± 1.06	3.83 ± 0.98	0.925
Mitral regurgitation grade	2.82 ± 1.1	0.51 ± 0.73	<b>&lt; 0.001</b>
RA area (cm <sup>2</sup> )	20.74 ± 9.02	14.03 ± 3.99	<b>&lt; 0.001</b>
Tricuspid annulus diameter (cm)	3.24 ± 0.7		
Tricuspid regurgitation grade	2.05 ± 1.06	0.5 ± 0.63	<b>&lt; 0.001</b>
TR gradient (mmHg)	45.12 ± 20.23	38 ± 8.48	0.139
RV end-diastolic area (cm <sup>2</sup> )	18.26 ± 7.2	19.66 ± 6.08	0.149
RV end-systolic area (cm <sup>2</sup> )	11.71 ± 5.12	13 ± 4.29	<b>0.032</b>
RV fractional area change (%)	36.2 ± 12.51	33.02 ± 11.99	0.101
RV long-axis (diastolic)	6.08 ± 0.89	6.31 ± 0.72	<b>0.034</b>
RV short-axis (diastolic)	3.54 ± 0.77	3.24 ± 0.48	<b>0.012</b>
RV sphericity index (diastolic)	1.75 ± 0.24	1.97 ± 0.25	<b>&lt; 0.001</b>

LV= left ventricle/ventricular; LA= left atrium; RV= right ventricle/ventricular;  
RA= right atrial; TR gradient= transtricuspid gradient.

**Table 6: Multivariate logistic regression analysis**

Variable	OR	[95% CI]	p-value
Age	0.875	[0.793 - 0.964]	<b>0.007</b>
ACEi/ARB	5.26	[0.903 - 30.628]	0.065
Baseline RVFAC	0.877	[0.801 - 0.961]	<b>0.005</b>

ACEi/ARB= angiotensin converting enzyme or angiotensin receptor blocking agent therapy; RVFAC= right ventricular fractional area change.

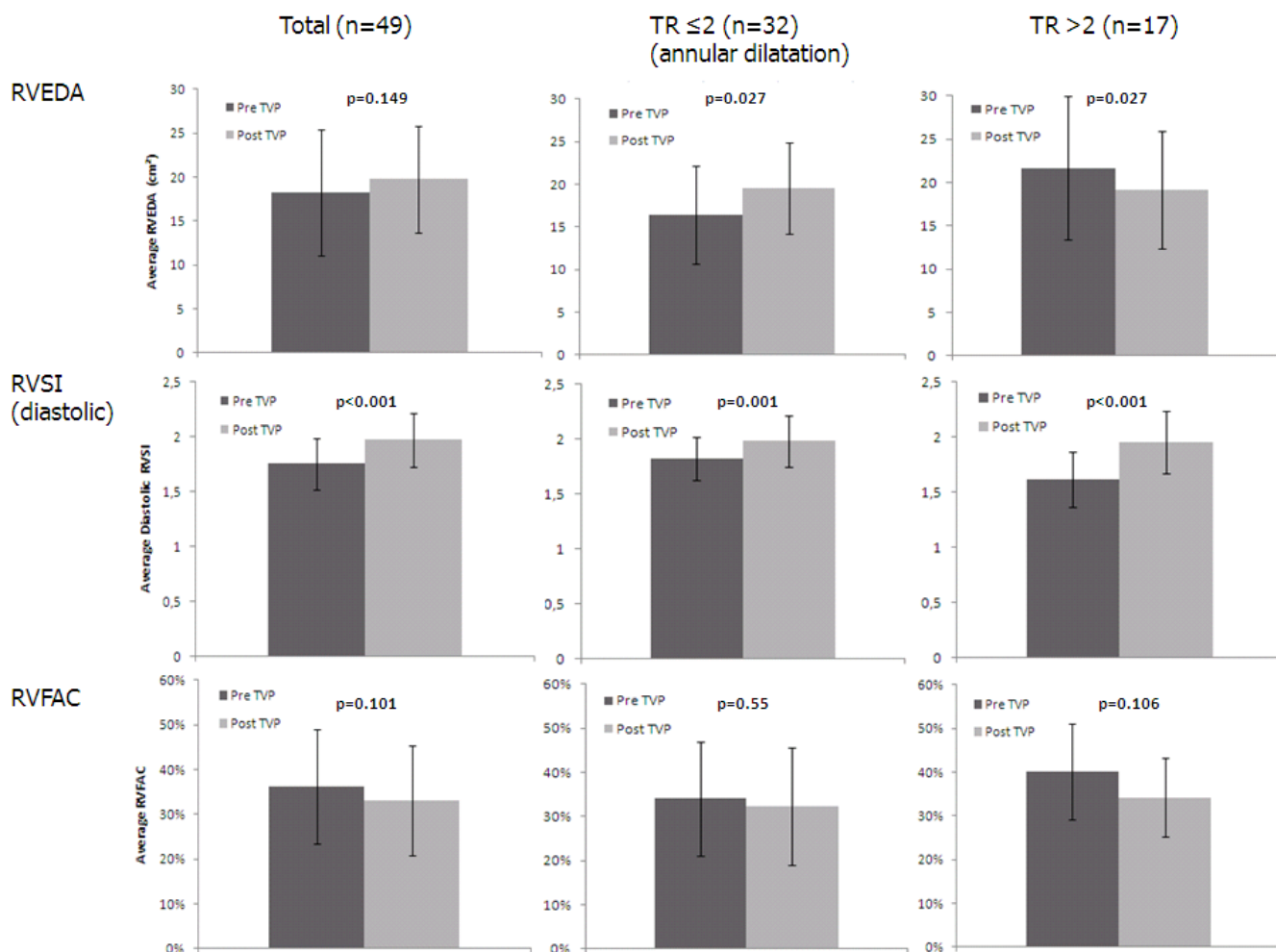


Figure 11: Echocardiographic evaluation of right ventricular end-diastolic area (RVEDA), RV end-diastolic sphericity index (RVSI) and right ventricular fractional area change (RVFAC) at baseline and follow-up in the entire study cohort (left panels), in the subgroup of patients with no significant ( $\leq 2$ ) TR but tricuspid annular dilatation (middle panels) and in the subgroup with more than moderate ( $> 2$ ) TR (right panels).

### 4.3 Discussion

Recent observations that TR does not always regress after successful mitral valve surgery and that late TR has an adverse impact on exercise capacity and outcome (49-52) has generally encouraged surgeons to routinely perform TVP at the time of left-sided heart surgery when severe co-existent TR is present. In 2005, Dreyfus et al. reported on 311 patients undergoing MVP, showing that remodeling annuloplasty of the tricuspid valve should be based on the presence of tricuspid annular dilatation rather than the grade of TR (21). Accordingly, guidelines on the management of valvular heart disease published in 2007 by the European Society of Cardiology underwent further refinement, recommending correction also for lesser degrees of TR in case of significant tricuspid annular dilatation (diameter  $> 40$  mm or  $> 21$  mm/m<sup>2</sup>) (29). Our center is an experienced tertiary care and referral service and historically one of the first to

judiciously implement these novel guidelines into daily clinical practice. Our findings clearly illustrate that as the indications for adding remodeling annuloplasty of the tricuspid valve to left-sided heart surgery have evolved, differential effects on RV size, geometry and function may be observed.

Contrary to what might have been expected, concomitant tricuspid valve surgery did not lead not to a reduction in RV size at short-term follow-up in the overall study population. The likely explanation for this finding is the fact that most patients in our study population underwent TVP because of TA dilatation rather than severe TR (65% vs. 35% respectively), also underscored by the fact that the average grade of TR severity was only 2 at baseline. Our findings indicate a significant correlation between the preoperative severity of TR and the subsequent change in end-diastolic RV size ( $r=0.5$ ,  $p=0.003$ ), and support previous findings by Kim et al. which showed that the extent of RV reverse remodeling post-TVP is directly proportional to the extent of RV volume overload prior to surgery (53). Indeed, in the subgroup of patients with more than moderate TR, the decrease in diastolic RV size after corrective TV repair became similar to what one would have expected on the basis of previous studies reporting on the hemodynamic effects of TVP in patients with severe TR (53,54). In contrast, patients with only mild TR at baseline exhibited a small but significant increase in end-diastolic RV volume after surgery. We speculate that this finding may be explained by the fact that all patients underwent TVP in addition to left-sided surgery, rather than isolated TVP. Once the left-sided lesion(s) has been addressed, an improvement in cardiac output may be expected, which in turn will lead to an increased RV preload and higher end-diastolic RV volumes, particularly in patients with lesser degrees of TR preoperatively. This subsequent rise in RV preload may be an important mechanistic cause of recurrent or progressive TR that is frequently observed late after mitral valve surgery, and constitutes the rationale for our surgeons to consider TVP in patients scheduled for left-sided heart surgery when TA dilatation is present, despite absence of significant TR.

Contrary to RV size, RV geometry did change significantly after surgery in the total study population. After TVP, positive remodeling of the RV took place, with the RV becoming more elliptical and less spherical as illustrated by the increase in RVSI (Figure 1). Not surprisingly, this process of reverse RV remodeling was most pronounced in the group of patients with more than moderate TR. This observation corroborates the findings by Reynertson et al, who reported on the adaptive changes in RV geometry in heart transplant patients following inadvertent endomyocardial biopsy disruption of the tricuspid apparatus (40). In that study, severe TR due to the development of a flail tricuspid valve did lead to a preferential dilatation of the RV in the free wall to ventricular septal axis. Our findings indicate that TVP may induce a “reshaping” of the RV, and abolish the asymmetric and spherical dilatation of the RV due to TR-related volume overload

which is most apparent at end-diastole. Restoring or preserving a normal RV shape and avoiding diastolic distortion of the interventricular septal geometry caused by RV volume overload may be an important factor in maintaining or improving LV preload and ejection fraction (55,56).

Shortly after TVP, RVFAC appears to decrease in many patients. However, this change did not reach statistical significance, not in the entire study population nor in any of the two subgroups (Figure 1). A decrease in right ventricular function post-TVP was anticipated, particularly in those with severe TR. RVFAC is an ejection phase index which tends to overestimate ventricular contractile function in the presence of severe TR because of favorable loading conditions stemming from an increase in preload and a decrease in afterload due to the low impedance of the RA. However, in this population undergoing TVP in addition to complex left-sided heart surgery, no difference was found in the postoperative change in RVFAC between patients with significant TR and those with TA dilatation and less severe TR. Substantial variance was found in the postoperative change in RVFAC between individual patients, with RV contractile force clearly improving in some and deteriorating in others. When we tried to discriminate the determinants of postoperative RV systolic function using multivariable analysis, only age and preoperative RVFAC emerged as predictive variables. This suggests that despite routine implementation of protective strategies to prevent myocardial ischemia during cardioplegic heart arrest, the RV in older patients may be more vulnerable to ischemia/reperfusion injury which is probably unavoidable during these prolonged procedures. Future studies should determine the impact of postoperative RV systolic dysfunction on the outcome of patients, and also evaluate whether “prophylactic” TVP is truly beneficial also in the older population scheduled for left-sided heart surgery.

Preoperative RVFAC was also significantly associated with the surgically induced change in RVFAC: a higher preoperative RVFAC was more likely to decrease post-TVP and vice versa. This finding confirms a previous observation in patients undergoing tricuspid valve surgery for severe isolated TR (54), and it can be explained by the fact that an already normal RVFAC value is unlikely to increase even more, particularly as the RV afterload may increase when tricuspid valve competence is restored. Conversely, in case of severe preoperative RV dysfunction and a dilated and geometrically distorted RV, reverse RV remodeling post-TVP will also be more extensive. As a consequence, RV wall stress (afterload) will decrease in these patients according to the Laplace equation, leading to an improvement in RVFAC. This explains why post-TVP RV function is most likely to improve in patients with a depressed RV function; this finding also shows a striking similarity to observations previously made in patients with degenerative MR and preoperative LV dysfunction scheduled for MVP (57). A decreased RV preoperative function should therefore not be a contraindication to TVP in patients with TA dilatation or significant TR that are scheduled for left-sided heart surgery.



## 5. General Conclusion

The addition of routine TVP in case of functional TR or TA dilatation, in comparison with standard MVP/MVR during complex left-sided surgery, is associated with a high risk of adverse events, especially with regards to heart failure hospitalizations, even in experienced hands and independent of most preoperative echocardiographic findings. Thereby, provides our study an important rationale for **no** routine addition of TVP in our patient population. Additionally, our observation that the EuroSCORE® more closely predicts 30-day mortality in patients undergoing TVP concomitant with MVP during complex left-sided heart surgery has never been reported before. The closer predictive value of the EuroSCORE® in patients with concomitant TVP is probably a reflection of the fact that the EuroSCORE® only accounts for “valve surgery” as such and not the “amount or complexity” of valve surgeries. Therefore, future risk-stratification models should take into consideration the number and complexity of valvular surgeries as well.

The effect of concomitant TVP on RV size and geometry in patients scheduled for left-sided heart surgery depends on the severity of preoperative TR. In those undergoing TVP because of TA dilatation rather than significant TR, RV sphericity decreases but RV size may increase at follow-up. In patients with more than moderate preoperative TR, RV size will decrease post-TVP, and RV sphericity will decrease even more compared to those with lesser degrees of TR. The preoperative degree of TR has no significant impact on postoperative RV systolic function. Additionally, older patients and those with higher preoperative RVFAC are more likely to develop a decrease in RV contractile function post-TVP.

Obvious limitations inherent to the retrospective study design should be considered when findings are interpreted. Also, our first study (Article: Clinical outcomes) was not a comparison of TVP vs. no TVP in patients with TA dilatation and/or more than moderate functional TR and overall surgical interventions did differ between both groups, with regard to additional CABG, aortic valve surgery, and MR etiology. Therefore, even though TVP+ patients had worse outcomes, the addition of TVP might still have prevented an even more infaust prognosis. Nevertheless the retrospective design, our findings of the second study (Article: RV function and geometry) are interesting because until now the effects of TVP in addition to left-side heart surgery have not been widely studied, particularly not in a population undergoing TVP because of TA dilatation rather than severe TR, or in patients scheduled for left-sided heart surgery other than mitral valve surgery alone. We acknowledge that follow-up duration was relatively short in our study and likely not enough to determine the long-term effects of TVP concomitant with complex left-sided heart surgery. It may also be argued that evaluation of RV function using 2-



dimensional echocardiography is problematic because of the complex RV geometry and the sometimes limited definition of the endocardial surface caused by heavy trabeculation. However, analysis was performed on images acquired by experienced personnel, and extreme care was taken to measure RVFAC (a parameter of RV function that is well-validated in many previous studies) from a true non-foreshortened apical 4-chamber view.

Regarding the limitations, careful interpretation of our findings should guide further prospective studies to examine the safety and efficacy of routine TVP in this vulnerable population, and to better characterize which patients might benefit most. Additionally, longer follow-up prospective studies using more sophisticated parameters than RVEDA or RVFAC (e.g. cardiac magnetic resonance imaging for serial assessment of RV volume and systolic function) are needed to evaluate the exact effect of TVP on RV size or function.

By this means, our hypothesis is only partly confirmed since the EuroSCORE® has a closer predictive value in patients with concomitant TVP, more preoperative echocardiographical parameters were expected to be found in relation to clinical outcomes and concomitant tricuspid valve surgery did not lead not to a reduction in RV size and systolic function at short-term follow-up in our overall study population.

## Acknowledgements

Making a senior thesis is far but a one man mission. Therefore, I want to use this page to thank everyone who helped me through these months of hard work.

First of all, I want to thank Hasselt University and Hospital Oost Limburg in general to give me the opportunity to start this project and make use of their facilities.

Special thanks to Prof. Dr. Mullens as promoter who supported me amazingly all the way and always made time for me even when he was on vacation. I think no one could ever have a greater promoter.

I want to thank Dr. Vandervoort and Dr. Verhaert who also guided me throughout the investigation process and giving me intensive feedback during writing. Thanks a lot!

Very special thanks to Rozette Reyskens for making time to analyze the echo images together with me. I know this analyzing work was not her favorite daily activity but nevertheless her enthusiasm was incredible. Besides that, also thanks for the nice talks and patience with me 😊.

The statistical analysis of this thesis could never made possible without the help of Yannick Vandendijck. I sincerely appreciate the help you offered me during your spare time. Thanks a lot.

I would like to thank the rest of "my colleagues" at the cardiovascular, surgical and echocardiographical department: Linda Jacobs, Jan Vercammen, Kristien Machiels, Kathleen Cuyvers, Lea Vanaken, Carlo Van Nieuwkerke, Hilde Gielen, Mathias Vrolix, Jo Dens, Patrick Noyens, Hugo Van Herendael, Maximo Rivero, Herbert Gutermann and Robert Dion!

Also thanks to my second examiner, Prof. Dr. Marc Hendrikx, and institutional supervisor, Prof. dr. Marjan Vandersteen, for reading this thesis.

Not to forget, I want to thank my parents, together with my brother and girlfriend, for their great support and the opportunity for letting me use the car every day!!

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## Supplemental Materials and Methods

Echocardiography is one of the most frequently used techniques for diagnosing cardiovascular diseases since real-time two-dimensional (2D) echocardiography provides high-resolution images of cardiac structures and their movement so that detailed anatomic and functional information about the heart can be obtained.

### ***Procedures to perform echocardiographic examinations***

Comprehensive 2D echocardiographic exams were performed with a commercially available system (Philips Medical Systems, Eindhoven, IE33®) by European Society of Echocardiography Registered Diagnostic Cardiac Sonographers. There were two kinds of echocardiographic examinations performed, transthoracic echocardiographic examinations (TTE) and transesophageal echocardiographic examinations (TEE). TTE is completely non-invasive, a transducer is placed directly on the chest while emitting harmless ultrasound beams to create an image. The patient was asked to pull out his/her shirt before laying in the appropriate left lateral decubitus position (Figure 1). ECG patches and electrodes were placed on the patient's body to monitor the heart rate in a standard manner. For proper movement of the transducer's tip and realizing a good image quality, a small amount of aquasonic ultrasound transmission gel was used.



Figure 1: Left lateral decubitus position for recording standardized echo images.

TEE on the other hand is a semi-invasive procedure because of a transesophageal probe intubation that can be uncomfortable in unprepared patients. Mostly, a TEE was performed in addition to a TTE to evaluate the mitral valve, left atrium (LA), atrial septal defects, endocarditis and its complications in more detail. The patient fasted for at least 4 hours before undergoing TEE, and a history of esophageal pathology was evaluated before. Patients with dentures removed these. An intravenous access for administration of contrast agent or medication was placed by qualified employees. Again, ECG patches and electrodes were placed on the patient's

body to monitor the heart rate. Immediately before intubation of the transesophageal probe, xylocaine spray (10%) was used to anesthetize the posterior pharynx locally. A short-acting sedative diprivan (1%), 1 to 10 mg, was mostly necessary to make the TEE examination more comfortable for the patient. This agent was used with caution because of potential respiratory suppression. No problems associated with this medication were noted during the investigations. A special TEE probe, with a transducer tip of 10 to 14 mm which can be maneuvered to various positions in the esophagus and the stomach, was used. Additionally, the multiplane transducer was able to rotate 180 degrees. All together, this allowed us to visualize the heart and other structures in a detailed manner. Rotation of the transducer was accomplished by a finger-pressure-sensitive switch at the proximal operator end.

The examination began with the patient in the left lateral decubitus position. To protect the TEE scope, a bit guard and a latex free cover was used. At probe introduction, the imaging surface of the transducer faced the tongue, which directs the ultrasound beam anteriorly toward the heart when the probe is in the esophagus. With guidance of the left index finger the transducer was advanced smoothly and slowly posteriorly toward the esophagus. At that time, the patient was asked to swallow. The tip of the TEE was advanced into the esophagus without force or significant resistance. From this point on the visualization started to evaluate the different heart structures. The used probe was cleaned afterwards with enzyme solution and glutaraldehyde disinfectant. Mostly, patients needed a recovery time after the procedure. The intravenous catheter was also removed when it was not applicable anymore for other procedures afterwards. The patients were told not to drive for 12 hours if sedation was used.

Typically, a TTE examination was initially performed by a echocardiographer/sonographer and required 20 to 30 minutes. Afterwards, these images were reviewed and supervised by a staff echocardiologist. A TEE examination was performed by a echocardiologist, assisted by a sonographer to sedate and hold the patient in the appropriate position during the examination. This procedure took 30 to 45 minutes.

### ***Recording echocardiographic images***

Echocardiography uses high-frequency ultrasound (2.0 to 7.5 MHz) to evaluate the structural, functional and hemodynamic status of the cardiovascular system. A 2D TTE was performed in a standard manner from three standard transducer positions: the parasternal, apical and subcostal windows. From each transducer position, multiple tomographic images of the heart relative to its long- and short-axis are obtained by manually rotating and angulating the transducer. The long-axis view bisects the heart from the base to the apex. The short-axis view is perpendicular to the long-axis view. M-mode echocardiography complements 2D echocardiography by recording detailed motions of cardiac structures. M-mode is used for the measurement of dimensions and is essential for the display of subtle motion abnormalities of specific cardiac structures. The hemodynamic status is evaluated by the use of the Doppler technique. Doppler echocardiography measures blood-flow velocities in the heart and great vessels and is based on the Doppler effect. The Doppler effect states that sound frequency increases as a sound source moves towards the observer and decreases as the source moves away. The most common uses of Doppler echocardiography are in the pulsed- and continuous-wave forms. In the pulsed-wave mode, a single ultrasound crystal sends and receives sound beams. The ultrasound is reflected from moving red blood cells and is received by the same crystal. In the continuous-wave mode, the transducer has two crystals: one to send and the other to receive the reflected ultrasound waves continuously. Additionally, blood flow can also be visualized with the color-flow imaging based on pulsed-wave Doppler principles. Blood flow directed toward the transducer is standard color-coded in shades of red. Blood flow directed away from the transducer is standard color-coded in shades of blue. Each color has multiple shades, and the lighter shades within each primary color are assigned to higher velocities. Optimization at the time of the examination was needed by using the optimal transducer, knob settings and transducer positions. Gray scales and gains were controlled manually to minimize background noise and to maximize the delineation of cardiac structures. The depth of the fields was also controlled to provide the optimal image size. Filter settings depend on the type of Doppler study and were selected automatically. These optimizations were important to make certain that the area of abnormal blood flow was not underestimated by a low gain setting or overestimated by a low filter setting, because severity of valvular regurgitation or shunt flow depends on the area of abnormal blood flow detected with color-flow imaging. The optimal setting displayed the entire flow jet with minimal background noise.



### ***Prospective study: Protocol RV function and geometry***

Normal echocardiographic analysis with special attention to endocardial delineation in LAX and 4-chamber view. Try optimise RV visualisation.

Additional: Do not forget **TAPSE RV** and **VCI**.

These measurements will be performed during the echocardiographical analysis, by this means you can see which parameters are important.

- Left ventricle (LV): left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD): LAX view.
- LV: diastolic dysfunction.
- Left atrium (LA): diameter in parasternal long-axis and in 4-chamber view (from the mitral valve tips to the upper part of the atria).
- LA: area (systole) and volume (systole en diastole): tracen in 4- and 2-chamber view.
- Mitral annulus: measure in systole and diastole in 4-chamber view.
- Left ventricular ejection fraction (LVEF): Teichholz in LAX view or Simpson (4- and 2-chamber) if no clear delineation is present.
- Mitral insufficiency: good visualisation of the proximal jet (PISA).
- Tricuspid valve: coaptation depth and tethering area (Figure 1, respectively A and B).

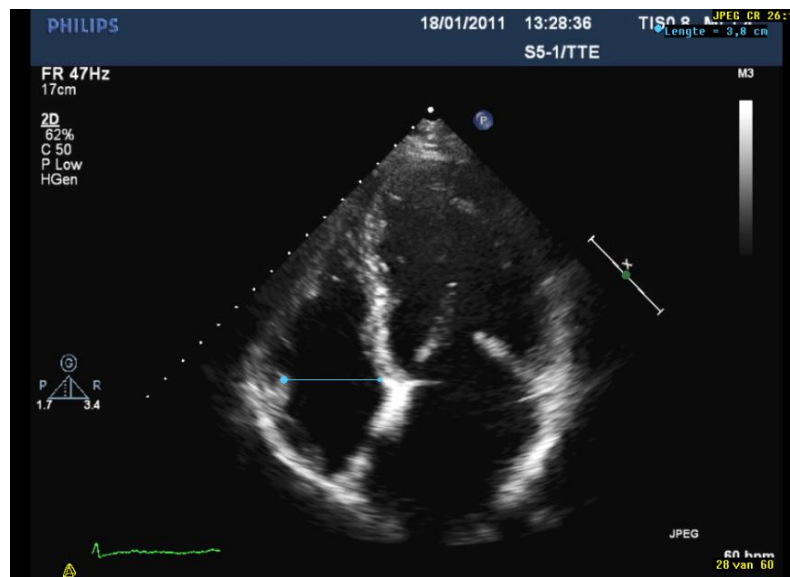
Figure 1:



- Right ventricular systolic pressure (RVSP) without right atrial pressure (RAP).
- Aortic stenosis (AS).
- Vena cava inferior (VCI) diameter.

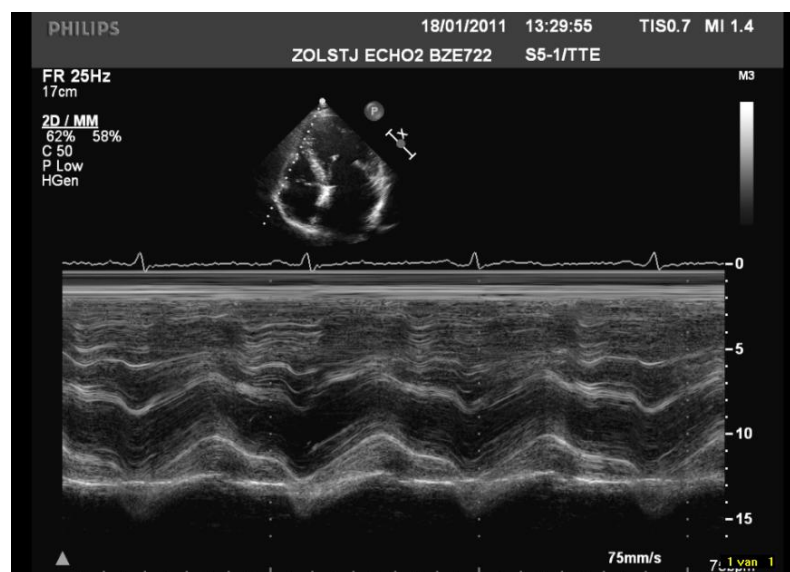
- Tricuspid annulus: in diastole (Figure 2).

Figure 2:



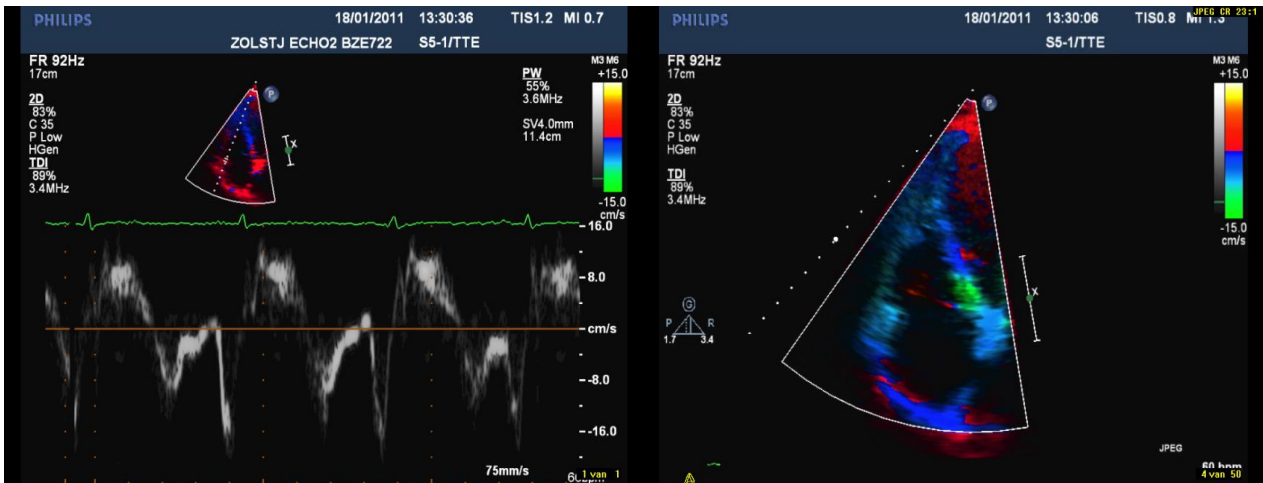
- Tricuspid Regurgitation (TR): Color doppler, determine jet area.
- Right ventricle (RV): TAPSE (Figure 3).

Figure 3:



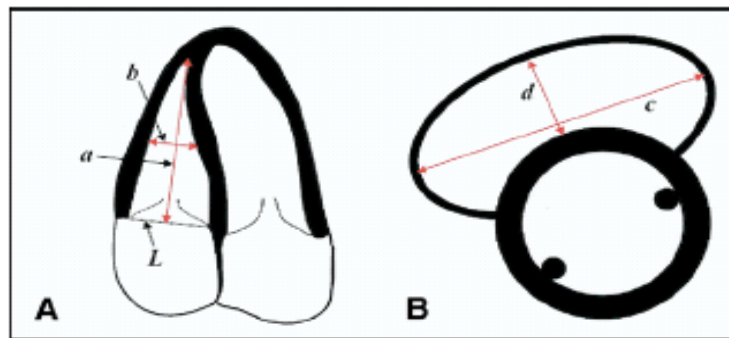
- RV: Zoom in (frame rate ↗).
- RV: TDI RV free wall (Figure 4).

Figure 4:



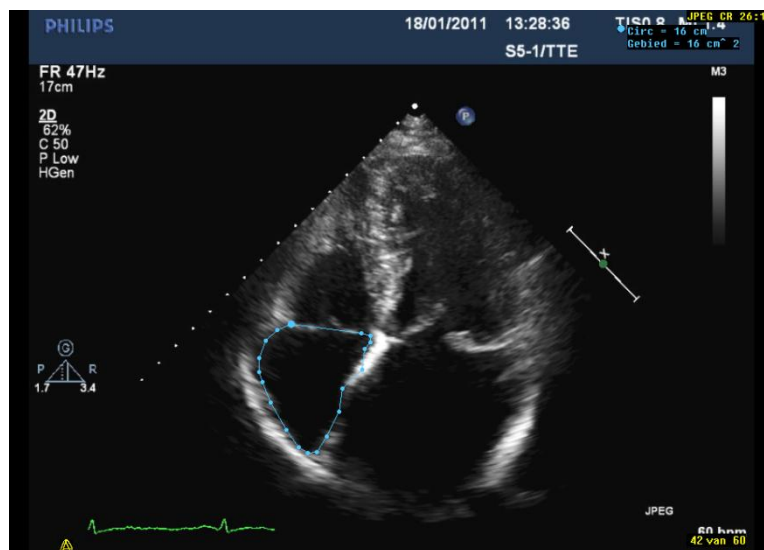
- RV: - Long-axis (a) and short-axis (b): 4-chamber view (Figure 5A).
- Longest lateral distance (c) and free wall - midseptal (d) (Figure 5B).
- Both in diastole and systole!

Figure 5:



- Right atrium (RA): area (Figure 6) and diameter in 4-chamber view.

Figure 6:



## Supplemental Results

**Table 1: Baseline medication**

	TVP -	TVP +	p-value
n	86	89	
ACEi/ARB	52.3%	60%	0.353
BB	65.1%	73.3%	0.216
Vasodilator	12.8%	16.7%	0.476
Ca-antagonist	15.1%	8.3%	0.239
Loop diuretics	53.5%	36.7%	<b>0.045</b>
Thiazide diuretics	14.0%	8.3%	0.321
Spironolactone	19.8%	11.7%	0.161
Statin	37.2%	65%	<b>0.001</b>
Warfarin	23.3%	11.7%	0.063
Aspirin	44.2%	70%	<b>0.001</b>
Digoxin	20.9%	11.7%	0.119

ACEi-ARB= Angiotensin converting enzyme or angiotensin receptor blocking agent therapy; BB= beta-blocking agents.

**Table 2 : Univariate logistic analysis**

Variable	OR	[95% CI]	p-value
Age	0.909	[0.849 - 0.974]	<b>0.007</b>
ACEi/ARB	3.343	[1.006 - 11.107]	<b>0.049</b>
Baseline NYHA class	1.387	[0.619 - 3.11]	0.427
Baseline RV diastolic area	0.941	[0.856 - 1.035]	0.213
Baseline RV systolic area	1.021	[0.912 - 1.143]	0.7168
Baseline RVFAC	0.896	[0.836 - 0.961]	<b>0.002</b>
Baseline RA area	0.928	[0.859 - 1.004]	0.061
Baseline LVEF	0.625	[0.013 - 29.838]	0.812
Baseline Long-axis	1.025	[0.59 - 1.778]	0.931
Baseline Short-axis	0.471	[0.173 - 1.281]	0.141
Baseline RVSI	1.012	[0.974 - 1.051]	0.541
Baseline TR grade	0.820	[0.473 - 1.422]	0.48
Follow-up TR grade	1.113	[0.450 - 2.751]	0.817
Baseline TR >2	0.483	[0.137 - 1.7]	0.257
Baseline TR gradient	1.012	[0.974 - 1.051]	0.541
Follow-up TR gradient	1.014	[0.928 - 1.109]	0.752
Difference TI gradient pre-post	0.999	[0.949 - 1.053]	0.98

**Type of surgery**

MVP vs MVR	2	[0.45 - 8.888]	0.363
AVR	0.536	[0.158 - 1.998]	0.374
CABG	0.9	[0.273 - 2.964]	0.863

**Duration of surgery**

Cross-clamp time	0.998	[0.985 - 1.012]	0.788
CPB time	1.004	[0.995 - 1.013]	0.424

ACEi/ARB= angiotensin converting enzyme or angiotensin receptor blocking agent therapy;  
 NYHA= New York Heart Association; RV= right ventricle/ventricular;  
 RVFAC= right ventricular fractional area change; RA= right atrial;  
 LVEF= left ventricular ejection fraction; RVSI= right ventricular sphericity index;  
 TR= tricuspid regurgitation; MVP= mitral valve repair; MVR= mitral valve replacement;  
 AVR= aortic valve replacement; CABG= coronary artery bypass grafting;  
 CPB= cardiopulmonary bypass.

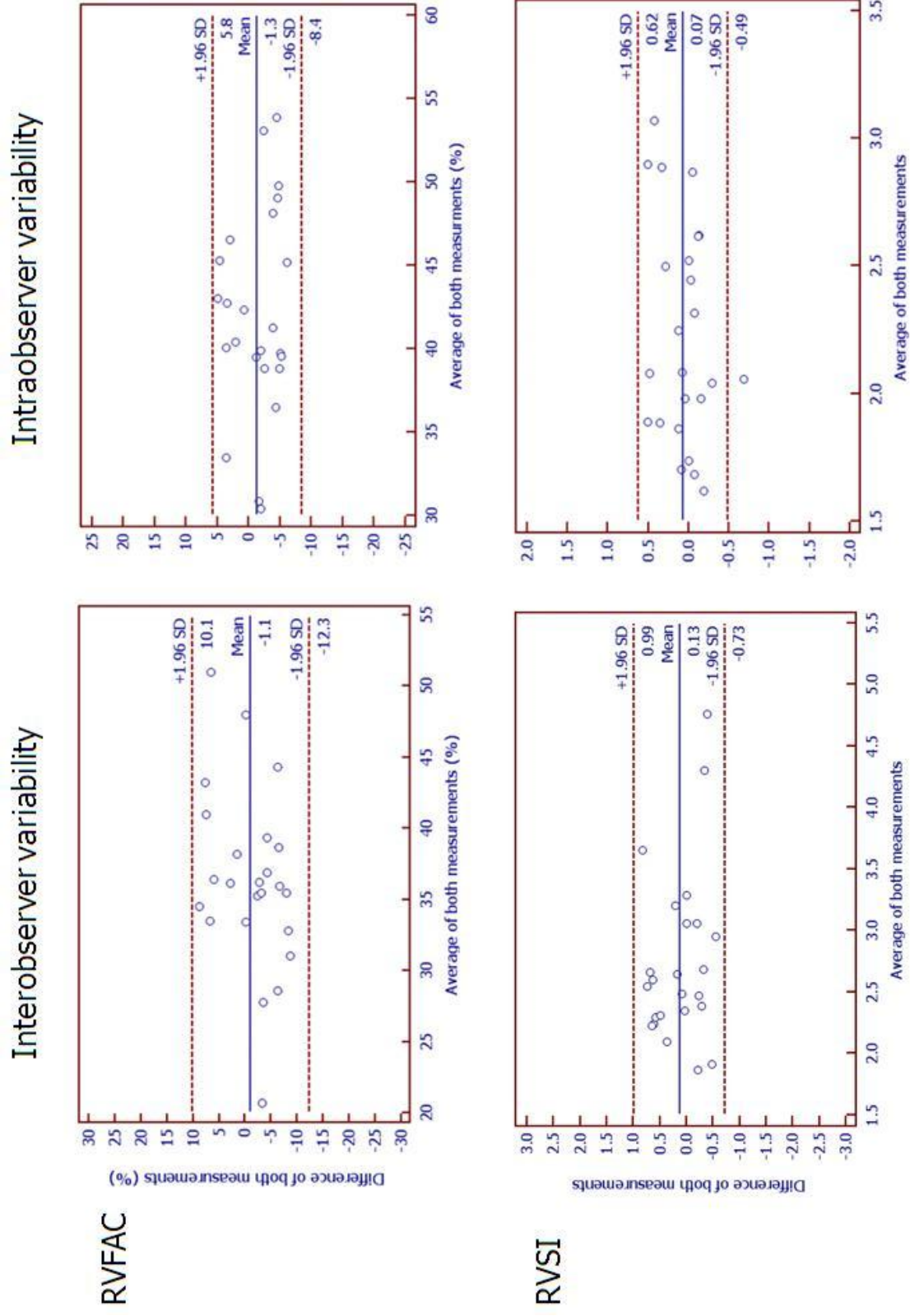


Figure 1: Bland-Altman plots showing inter- and intraobserver variability in measuring right ventricular fractional area change (RVFAC) and right ventricular sphericity index (RVSI).



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**Clinical outcomes and analysis of right ventricular function and geometry in patients undergoing tricuspid annuloplasty in addition to mitral valve surgery during complex left-sided heart surgery**

Richting: **master in de biomedische wetenschappen-milieu en gezondheid**

Jaar: **2011**

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