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## Characterization of tricuspid regurgitation and its prognostic implications

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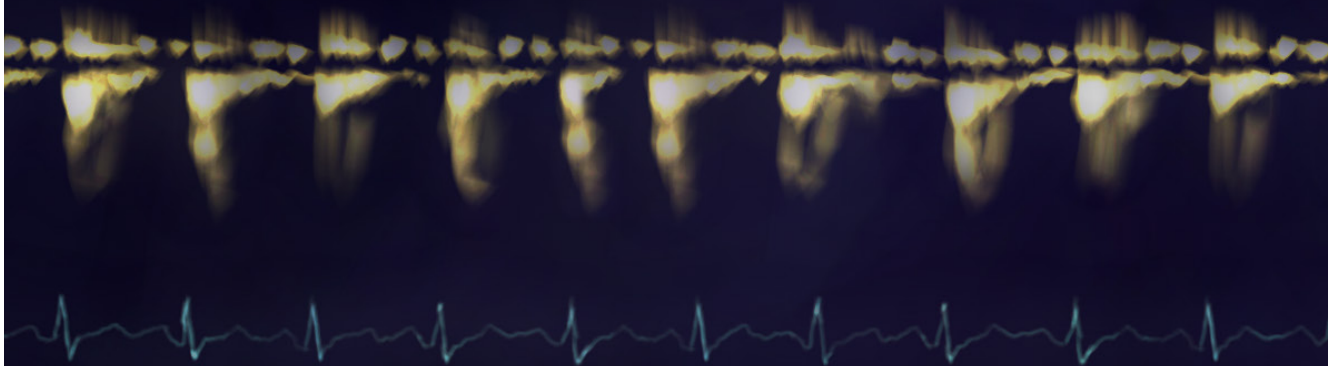
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# Chapter 1

## **General introduction and outline of the thesis**





## GENERAL INTRODUCTION

The tricuspid valve is often referred to as 'the forgotten valve', since it was virtually ignored by clinicians until the beginning of the 21st century. Known for much longer, tricuspid regurgitation – a disorder in which the tricuspid valve does not close properly, causing backward flow of blood - was first described by T.W. King in 1837. He found that distention of the right ventricle with water often caused substantial reflux through the tricuspid valve, while a similar procedure in the left ventricle would leave the mitral valve firmly closed (1). The conclusion that the tricuspid valve was physiologically weak to form a safety valve for the right ventricle was generally accepted, and for a long time tricuspid regurgitation was neglected while treatment for left valvular heart disease evolved (2). Unfortunately, tricuspid regurgitation has recently been demonstrated to be less harmless than had been thought. In 2004, Nath et al. (3) demonstrated that increasing tricuspid regurgitation severity was associated with worse survival in a large cohort of 5,507 war veterans. These results initiated extensive research, which has led to improved knowledge on the tricuspid valve and tricuspid regurgitation in the past two decades.

### Tricuspid valve anatomy

Situated between the right atrium and right ventricle, the tricuspid valve is the largest of the heart valves with an anatomical area of 4-6cm<sup>2</sup> (4). Its structure consists of the tricuspid annulus, the 3 leaflets, the chordae and the papillary muscles. The function of the valve depends on the cohesion and coordination of all these components.

A normal tricuspid annulus has a highly dynamic shape with changes in area exceeding 20% during the cardiac cycle, thus facilitating passive transfer of blood from the atrium to the ventricle (5, 6). This flexibility is enabled by the little fibrous tissue or collagen along the right ventricular free wall, which also causes it to be sensitive to dilation of the base of the right ventricle or the right atrium. The resulting tricuspid annular dilation may impede leaflet coaptation and therefore cause tricuspid regurgitation (6).

The 3 leaflets of the tricuspid valve (anterior, posterior and septal) are attached to the right ventricular free wall and the interventricular septum through chordae and papillary muscles. The septal and posterior leaflets are directly attached to the interventricular septum or to multiple small septal papillary muscles, as well as to the posterior papillary muscle. The large anterior papillary muscle is attached to the right ventricular free wall and supplies chordae to the anterior and posterior leaflets. In case of dilation of the right

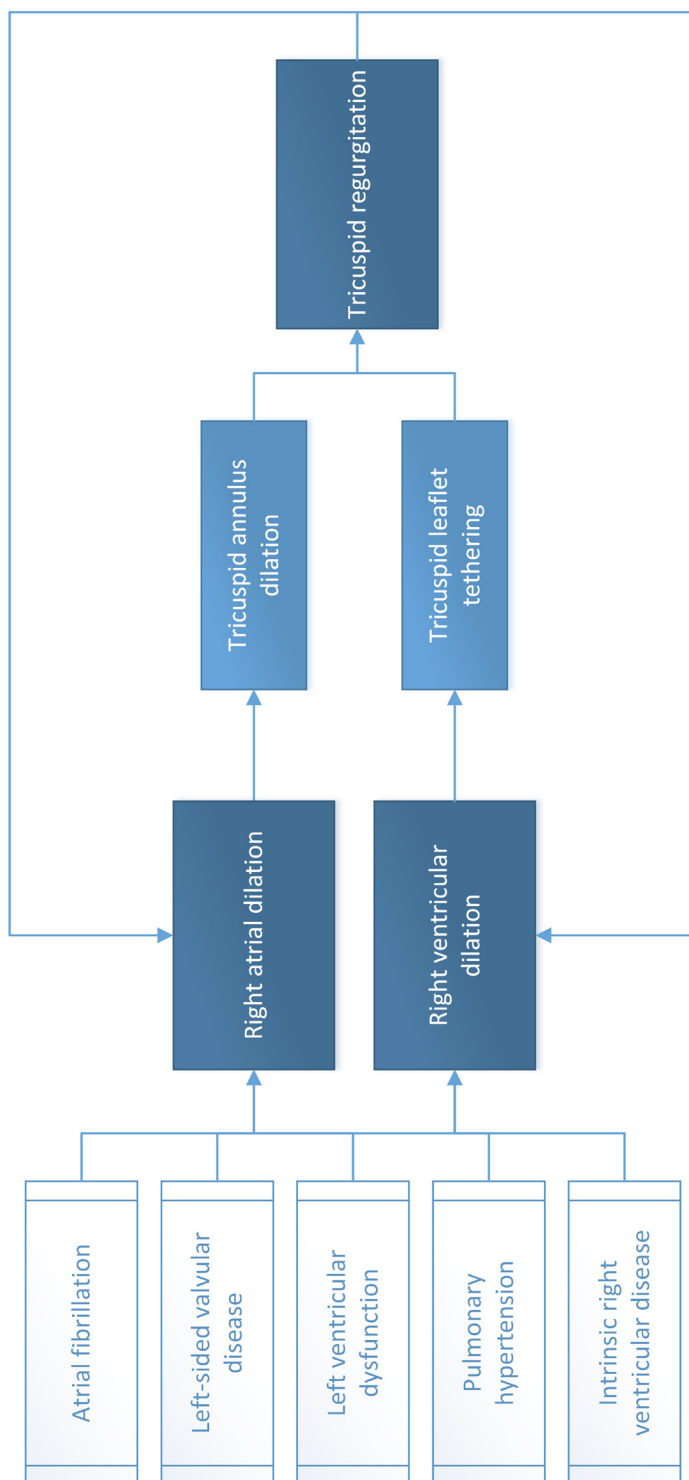
ventricle, stretching of the papillary muscles and chordae may cause leaflet tethering and subsequent tricuspid regurgitation due to reduced leaflet coaptation (6, 7).

### **Mechanisms of tricuspid regurgitation**

Tricuspid regurgitation is a heterogeneous disease which can be classified based on the underlying mechanism. Approximately 8-10% of all tricuspid regurgitation is primary, characterized by the presence of a primary abnormality of the tricuspid valve structure (8). Etiologies of primary tricuspid regurgitation include Ebstein's disease, infective endocarditis, valve prolapse, tumor, trauma and acute rheumatic disease.

The large majority of tricuspid regurgitation is secondary to conditions that cause tricuspid annulus dilation or leaflet tethering due to right ventricular or right atrial dilation, while the tricuspid valve apparatus is not primarily diseased (Figure 1). The conditions that can cause secondary tricuspid regurgitation are various and include left-sided valvular disease, myocardial disease associated with elevated left atrial pressures and pulmonary hypertension. All of these diseases cause right ventricular pressure overload. The right ventricle responds with myocardial hypertrophy and dilation to increase right ventricular preload and therefore maintain right ventricular systolic function (Frank-Starling law). However, as described in the previous paragraph, dilation of the right ventricle may lead to tricuspid annulus dilation and leaflet tethering which causes tricuspid regurgitation. The reflux of blood and volume overload induced by the tricuspid regurgitation leads to further right ventricular and atrial dilation, which worsens the existing tricuspid regurgitation due to further tricuspid annulus dilation and leaflet tethering in a vicious circle. Right ventricular dilation may eventually lead to right ventricular dysfunction (9, 10).

A type of secondary tricuspid regurgitation that is increasingly recognized as a separate entity is isolated tricuspid regurgitation, accounting for 6-10% of all significant (moderate or severe) tricuspid regurgitation (8, 11, 12). This form of tricuspid regurgitation differs from the above mentioned types of secondary tricuspid regurgitation by the absence of concomitant left-sided heart diseases or pulmonary hypertension. While the left-sided heart disease related types of tricuspid regurgitation have more prominent right ventricular dilation and tricuspid leaflet tethering, isolated tricuspid regurgitation mainly results from right atrial and tricuspid annulus dilation, as the right ventricular afterload is normal in these patients. Isolated tricuspid regurgitation is frequently associated with older age, the female sex and atrial fibrillation (13, 14). Because longstanding atrial fibrillation leads to right atrial enlargement and subsequent tricuspid annular dilation, various studies have suggested atrial fibrillation to be a major cause of isolated tricuspid regurgitation (15, 16). Nevertheless, atrial fibrillation and isolated significant tricuspid



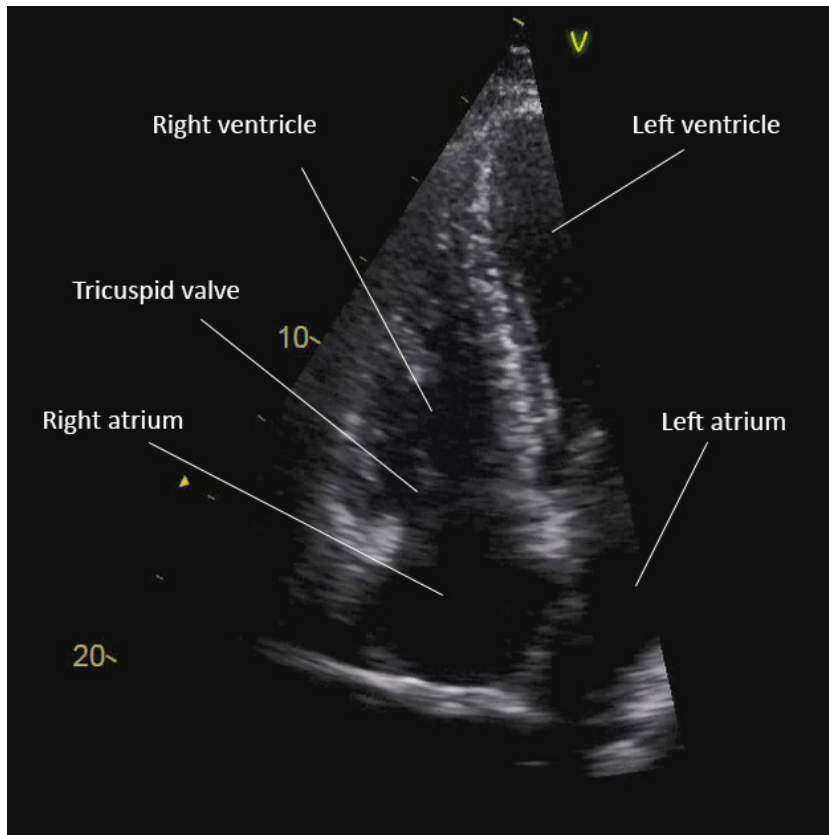
**Figure 1. Mechanisms of secondary tricuspid regurgitation**

regurgitation do not always coexist and other mechanisms such as a fibrous skeleton of the tricuspid annulus with less structural integrity or senescent annular degeneration may contribute to the development of isolated TR (14, 17).

### **Presentation and evaluation of tricuspid regurgitation**

Tricuspid regurgitation is a relatively common disease, with an estimated prevalence of moderate and severe tricuspid regurgitation of 0.5-0.8% in the general population, which increases with age (11, 18). The prevalence of concomitant tricuspid regurgitation in patients with mitral valve disease is >30% (19, 20). Mild tricuspid regurgitation is far more widespread in the general population (65-80%), but as mild tricuspid regurgitation is well tolerated and patients often remain completely asymptomatic in early stages of the disease, these patients often stay unnoticed (4). When tricuspid regurgitation severity progresses, morphological changes of not only the tricuspid valve, but of the complete right heart are related to the onset of symptoms: patients present with right heart failure. Right heart failure is a clinical diagnosis characterized by reduced exercise capacity and/or signs of right-sided decompensation in combination with structural and/or functional abnormalities of the right heart (21, 22). A decrease in cardiac output due to a leftward shift of the interventricular septum because of volume overload of the right ventricle is responsible for complaints of fatigue, exertional dyspnea and decreased functional capacity (21). Signs of right-sided decompensation are peripheral edema, abdominal fullness, congestive hepatomegaly and ascites. In the late stages of tricuspid regurgitation, severe venous congestion can lead to liver and renal dysfunction (23-25). Rarely, a holosystolic murmur can be heard upon physical examination (4).

Patients with tricuspid regurgitation can be evaluated with various non-invasive imaging techniques: 2-dimensional and 3-dimensional transthoracic or transesophageal echocardiography, magnetic resonance imaging, and computed tomography imaging. Currently, transthoracic 2-dimensional echocardiography is the technique of choice for the initial evaluation of the etiology and the severity of tricuspid regurgitation, and therefore used in the current thesis (Figure 2). As described in the current recommendations, tricuspid regurgitation can be graded as none/trivial, mild, moderate and severe by a multiparametric, integrative approach based qualitative, semiquantitative and quantitative color Doppler flow data, continuous-wave Doppler data of the regurgitant jet, and assessment of the right atrial and right ventricular dimensions (26, 27). As the pathophysiology of tricuspid regurgitation involves a complex interaction between the tricuspid valve, the right side of the heart and the pulmonary vasculature, echocardiographic evaluation of tricuspid regurgitation should not only include grading the



*Figure 2. Visualization of the right heart and the tricuspid valve on a right ventricle-focused apical 4-chamber view on 2-dimensional transthoracic echocardiography*

severity, but also visualizing the tricuspid annulus and leaflets, assessing right ventricular size and function, and estimating right atrial filling pressures.

Certain limitations in the assessment of tricuspid regurgitation by 2-dimensional transthoracic echocardiography should be considered. Identifying the leaflets of such a complex 3-dimensional structure with strong anatomical variations is challenging on transthoracic echocardiography. In case of poor quality views or endocarditis, transesophageal echocardiography may be required to better visualize the tricuspid leaflets. Transesophageal echocardiographic imaging also plays an essential role in guiding transcatheter interventions. Furthermore, 2-dimensional transthoracic echocardiography may underestimate the tricuspid annulus diameter (28) and vena contracta area (29). Use of 3-dimensional echocardiography and computed tomography may allow more accurate

measurements of the tricuspid annular shape, size, and function (6). Integration of cardiac magnetic resonance imaging, as gold standard to assess right ventricular morphology and function, may likewise be of additive value in the evaluation of tricuspid regurgitation (4).

### **Natural history of tricuspid regurgitation**

Trivial or mild tricuspid regurgitation, usually regarded as benign, may progress into significant (moderate or severe) tricuspid regurgitation over time due to the vicious circle of volume overload that enhances right ventricular dilation and dysfunction, which again worsens the tricuspid regurgitation. Factors associated with a fast development of significant tricuspid regurgitation are older age, the presence of a pacemaker or defibrillator lead, right ventricular dilation and dysfunction and left-sided valve surgery without concomitant tricuspid surgery (30). If left untreated, tricuspid regurgitation is independently associated with increased mortality, as was demonstrated by several natural history studies (3, 31). However, prognosis of patients with tricuspid regurgitation is confounded by the etiology of tricuspid regurgitation and the patient's comorbidities and hemodynamic profile. Some even claim that secondary tricuspid regurgitation, in the context of other cardiac diseases, is not the cause of worse prognosis, but a surrogate for the associated comorbidities (32). Right ventricular dilation and dysfunction are also thought to play an important role in outcome of patients with secondary tricuspid regurgitation, but results in various patient populations have been inconsistent (25, 33, 34).

Isolated tricuspid regurgitation has a better prognosis compared to other types of secondary tricuspid regurgitation, due to the lack of left-sided cardiac comorbidities (11). Nevertheless, even isolated tricuspid regurgitation seems to adversely impact prognosis, although studies are scarce and significant variation in the definition of isolated TR challenge the interpretation of discrepant results (35-37).

Regarding primary tricuspid regurgitation, Messika-Zeitoun et al. (38) demonstrated an excess of mortality and morbidity in patients with significant tricuspid regurgitation caused by flail leaflets, which could be improved by surgical treatment.

### **Treatment of tricuspid regurgitation**

Conservative treatment of tricuspid regurgitation includes optimization of right ventricular preload and afterload and targeting the underlying etiology (39). Although diuretic use may improve symptoms and reduce right heart failure hospitalizations, it is unclear if they alter the progression of tricuspid regurgitation and improve survival of patients (12, 40). Therefore, tricuspid valve surgery is the designated therapy for tricuspid regurgitation.

However, less than 5% of patients with severe tricuspid regurgitation are estimated to receive surgical intervention (41, 42). This low referral rate is most probably caused by lack of clear guidelines, a paucity of supportive data and reported in-hospital mortality rates for isolated tricuspid valve surgery as high as 8.8% (6, 12, 43). Nevertheless, European and American guidelines for the management of tricuspid regurgitation agree that severe tricuspid regurgitation should be treated at the time of left-sided heart valve surgery (class IC indication – level of evidence C) (39, 44). Even mild or moderate tricuspid regurgitation in the presence of a tricuspid annulus of >40mm should be considered to treat during left-sided heart valve surgery (class IIA indication - level of evidence B/C) (39, 44). This recommendation is based on data that concomitant preventative tricuspid valve surgery at the time of mitral valve surgery may prevent the development of significant tricuspid regurgitation and improve clinical outcome, although long-term outcome data are lacking (45-47).

Indications for isolated tricuspid valve surgery are even less well supported by the literature (class IIB indications – level of evidence C). The decision to intervene in tricuspid regurgitation patients that do not require left-sided heart valve surgery mostly depends on the presence of right ventricular dilation and dysfunction and the presence of symptoms of right heart failure (44). Current guidelines advise to intervene before the development of severe right ventricular dysfunction. However, the paucity of supportive data and high in-hospital mortality rates leads to significant delay in referral by clinicians, even though recent studies have shown that an acceptable mortality rate can be reached in patients without RV dysfunction or pulmonary hypertension (48). Axtell et al. (49) showed that 72% of patients with tricuspid regurgitation had evidence of right heart failure at the time of diagnosis, but that more than a quarter experienced a delay of more than a year before surgical referral.

Transcatheter therapies are currently being investigated as alternatives to surgical approaches in high-risk patients. Early outcome data provide some insight into the feasibility, safety, and efficacy of a variety of devices for percutaneous tricuspid valve replacement or repair (50-52). Although the results of these prospective trials are promising, they also demonstrate that defining the appropriate patient population for each transcatheter device as to achieve procedural success remains a challenge. Ongoing and future clinical research are of utmost importance to refine our understanding of the pathophysiology, progression, and prognostic impact of tricuspid regurgitation in order to optimize timing of surgery or transcatheter intervention and improve outcome in these patients.

## OBJECTIVE AND OUTLINE OF THIS THESIS

The aim of this thesis is to provide new insights in the characterization of tricuspid regurgitation and its clinical and prognostic implications. Part I of the thesis focusses on the relationship between secondary tricuspid regurgitation and the right ventricle. In chapter 2, the relation between right ventricular remodeling and survival in patients with significant secondary tricuspid regurgitation is assessed. Chapter 3 demonstrates the prognostic impact of a staging system for right heart failure, which combines right ventricular dysfunction with clinical signs of right heart failure, in patients with significant secondary tricuspid regurgitation. Chapter 4 evaluates the long-term impact of concomitant preventative tricuspid valve annuloplasty at the time of mitral valve annuloplasty on right ventricular remodeling in patients with primary mitral regurgitation.

Part II is designated to various types of tricuspid regurgitation in specific patient populations. In chapter 5, the prognostic impact of significant isolated tricuspid regurgitation in patients with atrial fibrillation is investigated. Chapter 6 reports on differences between men and women in the etiology and prognosis of significant tricuspid regurgitation. Chapter 7 provides more insight in the impact of increased body mass index on right ventricular remodeling and prognosis in patients with significant tricuspid regurgitation.

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