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Characterization of tricuspid regurgitation and its prognostic implications

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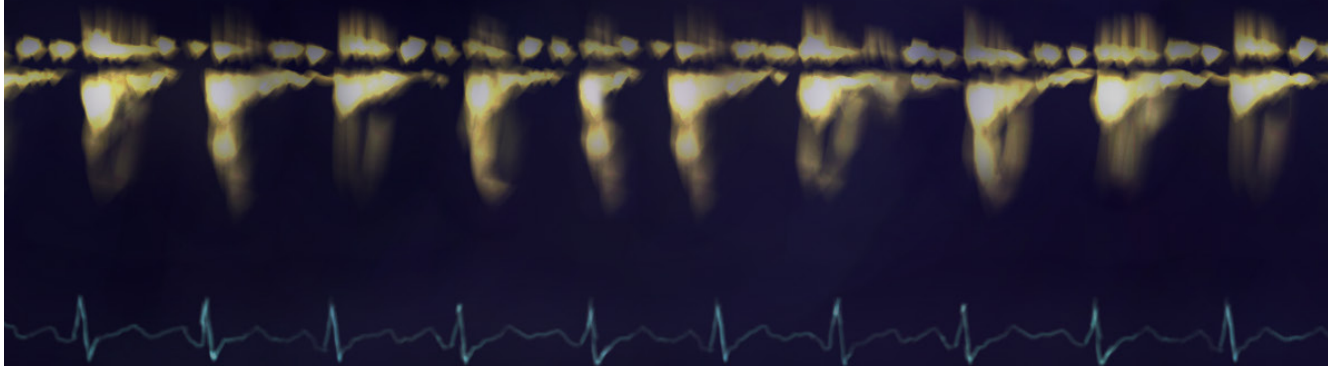
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Chapter 8

**Summary, conclusions and future
perspectives**

**Samenvatting, conclusies en
toekomstperspectieven**



SUMMARY

The introduction of this thesis (**chapter 1**) provides a state-of-the-art on tricuspid regurgitation encompassing current evidence on epidemiology, mechanisms of disease, clinical presentation, evaluation, prognosis and treatment. New, minimally invasive, transcatheter techniques have demonstrated to be safe and effective in reducing tricuspid regurgitation and improving symptoms of patients with severe tricuspid regurgitation that were not eligible for surgical valve repair or replacement. These achievements have led to increased awareness among clinicians of the burden of severe tricuspid regurgitation in the general patient population and underscore that severe tricuspid regurgitation should not be neglected and should be timely treated.

Understanding tricuspid regurgitation begins with knowledge of the anatomy of the tricuspid valve and the mechanisms behind tricuspid regurgitation. In chapter 1, differences between mechanisms and characteristics of different types of tricuspid regurgitation are described. In addition, the role of echocardiography in the assessment of tricuspid regurgitation severity is introduced. What is currently known about the adverse impact on prognosis and the treatment options for tricuspid regurgitation are also presented. The aim of the current thesis is to increase the understanding of the disease by characterizing tricuspid regurgitation in relation to the right ventricle and the clinical context and by evaluating the associated prognostic implications.

Part I: the right ventricle in secondary tricuspid regurgitation

The first part of the thesis focusses on the relationship between secondary tricuspid regurgitation and the right ventricle. It is known that the right ventricle plays an important role in the vicious circle that causes, maintains and worsens tricuspid regurgitation. It has also been suggested that right ventricular dilation and dysfunction influence prognosis in patients with tricuspid regurgitation.

The aim of **chapter 2** was to characterize right ventricular remodeling and assess the prognostic impact of right ventricular dilation and dysfunction on long-term survival in a large cohort of patients with significant (moderate and severe) secondary tricuspid regurgitation. Patients were divided into four different patterns of right ventricular remodeling according to the presence or absence of right ventricular dilation (defined as a tricuspid annulus diameter ≥ 40 mm) and dysfunction (defined as a tricuspid annular plane systolic excursion < 17 mm) at the first diagnosis of significant tricuspid regurgitation by transthoracic echocardiography. A combination of right ventricular dilation and dysfunction was present in 43% of the patients. At long-term follow-up, right ventricular

systolic dysfunction was independently associated with worse survival, regardless of the presence of right ventricular dilation.

Chapter 3 builds on the knowledge gained by the previous study. While the prognostic impact of right ventricular dysfunction had been established, the value of adding symptoms of right heart failure in the assessment of prognosis in patients with significant tricuspid regurgitation had never been investigated. In this study, 4 stages of right heart failure were defined in a population of patients with significant secondary tricuspid regurgitation. Patients in stage 1 had a preserved right ventricular function and no signs of right heart failure. In stage 2, patients had right ventricular dysfunction without symptoms of right heart failure. Stage 3 included patients with right ventricular dysfunction as well as right heart failure symptoms and patients in stage 4 presented with right ventricular dysfunction and refractory signs of right heart failure. Higher stages of right heart failure were independently associated with higher all-cause mortality at long-term follow-up. The introduction of this staging system in clinical practice could therefore be potentially valuable in risk stratification of patients with significant secondary tricuspid regurgitation.

Tricuspid valve annuloplasty during left-sided valve surgery is demonstrated to prevent development of significant tricuspid regurgitation and right ventricular dilation directly after surgery. The objective of the study presented in **chapter 4** was to extend this knowledge by assessing the long-term impact of preventative tricuspid valve annuloplasty during mitral valve surgery in patients with primary mitral regurgitation, a dilated tricuspid annulus ($\geq 40\text{mm}$) and no to mild tricuspid regurgitation. The results show that patients who received tricuspid valve annuloplasty had less right ventricular dilation and less severe tricuspid regurgitation at long-term follow-up. No significant differences in clinical outcome variables, such as all-cause mortality, surgical reintervention, heart failure hospitalization and pacemaker implantation, were demonstrated between patients with and without tricuspid valve annuloplasty, but as the sample size was relatively small, further randomized controlled trials are needed to establish the clinical relevance of preventative tricuspid valve annuloplasty during mitral valve annuloplasty in patients with primary mitral regurgitation.

Part II: tricuspid regurgitation in specific patient populations

In the second part of this thesis, various types of tricuspid regurgitation in specific patient populations are characterized. Tricuspid regurgitation is a heterogeneous disease and prognosis strongly depends on the etiology and clinical context. Therefore, it is important to investigate the clinical and echocardiographic characteristics and prognostic implications of significant tricuspid regurgitation in distinct populations.

In **chapter 5**, differences between men and women in characteristics and prognosis for all etiologies of tricuspid regurgitation are compared. Tricuspid regurgitation etiologies were defined as primary, left valvular disease related, left ventricular dysfunction related, pulmonary hypertension related, or isolated. The etiology of tricuspid regurgitation in women was more often left valvular disease related and isolated whereas men more often had left ventricular dysfunction related tricuspid regurgitation. In the total population, women had better 10-year survival compared to men. After propensity score matching, the influence of sex on survival was neutralized, but the tricuspid regurgitation etiologies remained significantly associated with all-cause mortality. Patients with significant tricuspid regurgitation related to left valvular disease or left ventricular dysfunction had lower survival compared to patients with primary tricuspid regurgitation. Etiology-specific approaches to detection and management of significant tricuspid regurgitation may improve prognosis in both men and women.

Chapter 6 focusses on isolated tricuspid regurgitation in patients with atrial fibrillation. By definition, these patients are free of left-sided heart diseases and pulmonary hypertension. Clinical and echocardiographic characteristics as well as long-term prognosis were compared between age- and gender matched patients with and without significant isolated tricuspid regurgitation. Atrial fibrillation patients with moderate or severe tricuspid regurgitation showed more right atrial dilation and right ventricular conical remodeling than atrial fibrillation patients without significant tricuspid regurgitation. Furthermore, significant isolated tricuspid regurgitation was independently associated with worse long-term prognosis in terms of all-cause mortality, heart failure hospitalizations and stroke. These results emphasize the need for prospective studies investigating the effect of early intervention in patients with atrial fibrillation and significant isolated tricuspid regurgitation.

In **chapter 7**, the impact of body mass index on right ventricular remodeling and prognosis in tricuspid regurgitation is investigated. A large cohort of patients with moderate and severe tricuspid regurgitation was divided into 3 groups according to body mass index: normal weight (body mass index 18.5-24.9 kg/m²), overweight (body mass index 25-29.9 kg/m²) and obese (body mass index ≥30kg/m²). Underweight patients and those with active endocarditis or peripheral edema at baseline were excluded. Overweight and obesity were associated with more pronounced right ventricular dilation compared to normal weight patients. This right ventricular remodeling appears to be adaptive, as no significant differences across body mass index groups were observed in right ventricular

systolic function. Additionally, higher body mass index was independently associated with better survival during long-term follow-up, also known as the 'obesity paradox'.

CONCLUSIONS AND FUTURE PERSPECTIVES

The impact of tricuspid regurgitation in the general community should not be underestimated. Tricuspid regurgitation is typically a disease of the elderly in an ageing world population. Furthermore, the results of the current thesis demonstrate the adverse prognostic impact of moderate and severe tricuspid regurgitation in various contexts.

Two-dimensional transthoracic echocardiography is the preferred imaging method to diagnose tricuspid regurgitation and evaluate the associated right ventricular remodeling, since it is widely available, non-invasive and inexpensive. However, advanced imaging techniques like 3-dimensional echocardiography are emerging and may become the standard procedure to accurately measure tricuspid regurgitation severity and the interaction with the right heart. Assessment of this interaction is of utmost importance, as the right ventricle plays an essential role in the pathophysiology and outcome of tricuspid regurgitation. The development of right ventricular dilation and consequently significant tricuspid regurgitation can be prevented in patients with a dilated tricuspid annulus by performing tricuspid annuloplasty during left valvular surgery. Unfortunately, timing of intervention in patients who already show significant tricuspid regurgitation and right ventricular remodeling has proven difficult, and the high mortality rates after tricuspid valve surgery in current clinical practice demonstrate that we are often too late. The question remains: how early should we intervene in severe tricuspid regurgitation?

In patients with significant tricuspid regurgitation, right ventricular systolic dysfunction is associated with worse prognosis. The presence of symptoms of right heart failure further indicates the risk of mortality in these patients. Incorporation of stages of right heart failure in future risk stratification of patients with significant secondary tricuspid regurgitation may help to identify patients who will benefit from earlier tricuspid intervention. However, validation of this staging system in a broader perspective is needed, as prognosis of significant tricuspid regurgitation is strongly dependent on the etiology and patient characteristics. Appropriate patient selection is key in successful treatment, whether by surgery or transcatheter interventions.

A number of transcatheter tricuspid valve repair devices are currently under investigation. The first results of these studies are promising. Transcatheter therapy may be a solution

for high risk patients with tricuspid regurgitation in the near future, although additional long-term outcomes are needed.

In conclusion, treating patients with tricuspid regurgitation is challenging, but with ongoing and future research on etiology-specific evaluation, advanced imaging techniques, appropriate patient selection for intervention and new therapies, prognosis of patients with significant tricuspid regurgitation can be improved.