Chapter 3
Tricuspid Regurgitation in Patients with Heart Transplant

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Abstract In this chapter, an overview of the epidemiology, the pathophysiology, the clinical features, management and prognosis of tricuspid regurgitation in patients post heart transplant will be discussed. An overview of the natural history of severe tricuspid regurgitation and treatment options will be illustrated via a clinical case.

Keywords Tricuspid • Regurgitation • Heart transplant • Echocardiography • Therapy • Outcome

Introduction

Tricuspid regurgitation (TR) is one of the common cardiac complications post heart transplantation (HTx)**,** potentially jeopardizing the long-term outcome and survival. However, despite existence of the clinical problem from the beginning of the HTx era in the early 80s, the appropriate approach for clinical management is yet not established. In this chapter, we present a clinical case with severe post-HTx TR, in which for a long time a surgical approach was postponed by the patient, illustrating the natural history of severe TR with all the potential cardiac and extra-cardiac complications. Thereafter, we provide an overview of the pathophysiology, the epidemiology, the clinical features, management and prognosis of TR according the current literature combined with our clinical experience as a medium sized HTx center since 1984.

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Case

Mrs. A underwent HTx in 1994, at the age of 32 years, because of severe chronic heart failure due to dilated cardiomyopathy, from which she was suffering since 1990. In 2012, pathogenic phospholamban mutation was found as the aetiology of her familial dilated cardiomyopathy. In the first year after transplantation, she was treated for three episodes of acute cellular rejection. From the first year on she was known with severe TR with partial prolapse due to chordae rupture, probably a complication of several surveillance endomyocardial biopsies (EMB's). The right atrium (RA) and right ventricle (RV) was severely dilated, but with preserved systolic function. The left ventricular function was normal, but the septum movement was paradoxal. The liver veins and vena cava inferior (VCI) were also dilated (30 mm), and TR peak velocity of 2.2 m/s. The hepatic veins Doppler showed systolic reversal. From 1994 to 2008 she remained reasonably well compensated with a good quality of life.

In 2008 she developed paroxysmal atrial tachycardia, along with progression of the right-sided congestion. Low doses of furosemide, metoprolol and later on flecainide was started. Because of syncope due the asystole's in 2009, a DDI-pacemaker was implanted. In the same year, electrophysiological ablation of the paroxysmal atrial tachycardia were performed. In the years following, she was relatively stable with low dose furosemide. Her echocardiography in 2010 showed persistent RV dilatation, severe RA dilatation and severe TR. The VCI was unvaried dilated (33 mm), barely collapsing. Her estimated systolic RV pressure was 39 mm Hg.

In 2014, she had more and more complaints of fatigue, right-sided congestion and slowly deterioration of her renal insufficiency and liver enzymes (see Fig. 3.1a and b). She had an evident progression of the TR severity with an estimated systolic RV pressure of 56 mm Hg. Her case was extensively discussed in the transplant team and a tricuspid valve surgery advised. The patient however was very reluctant about a major cardiac surgery and asked a second opinion in another heart centre. Their advice was however the same, but the patient remained dismissive of the operation.

In June 2016, she was admitted with severe heart failure and progression of her renal insufficiency. The electrocardiogram (see Fig. 3.2) of the severe TR patient at the latest follow-up, showing prominent right bundle branch block with right sided strain pattern, present from the very early in the course of the heart transplantation. She was treated with intravenous inotropic and diuretics and heart failure symptoms could be fairly compensated. However, this was at the expense of her renal function, with estimated e-GFR values of 20—30 mL/min, only with the support of continuous intravenous inotropics. On the other hand, without inotropic support, her renal functions deteriorated to e-GFR 15 mL/min and her symptoms escalated. After extensive discussion with the patient and family, we decided at last for tricuspid valve surgery. This was done in July 2016, with a valve replacement by a bioprothesis. The postoperative period was complicated by transient delirium and acute

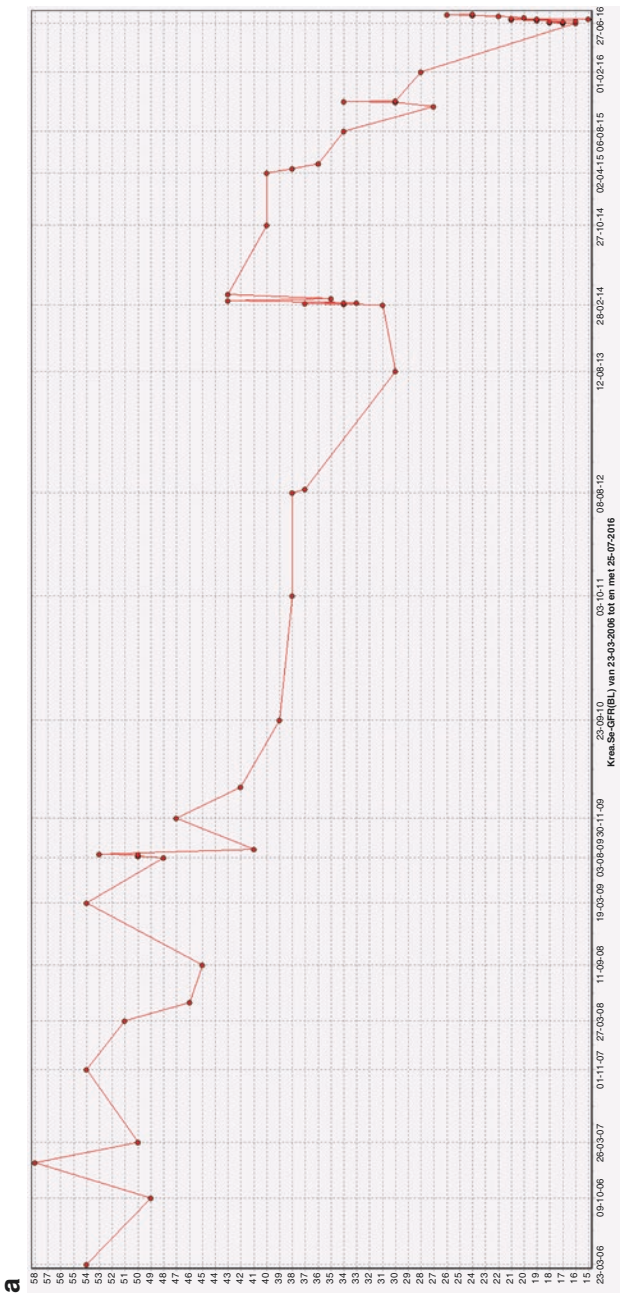

Fig. 3.1 (**a**) The e-GFR in the last 10 years. The renal function is progressively deteriorating albeit the clinical symptoms of right sided heart failure were present only during the last couple of years. (**b**) The cours of gamma-GT in the last 10 years. It's the most reliable parameter, like the e-GFR for the cardiorenal syndrome, for the cardio-hepatic syndrome as the right sided heart failure/chronic hepatic congestion over time progress. (**c**) The classical heart failure biomarker is less reliable in the setting of chronic right sided heart failure as a marker of the progression. The NT-proBNP is chronically 20–25 times the normal value ($N < 14$) elevated, but escalated very late in the disease course

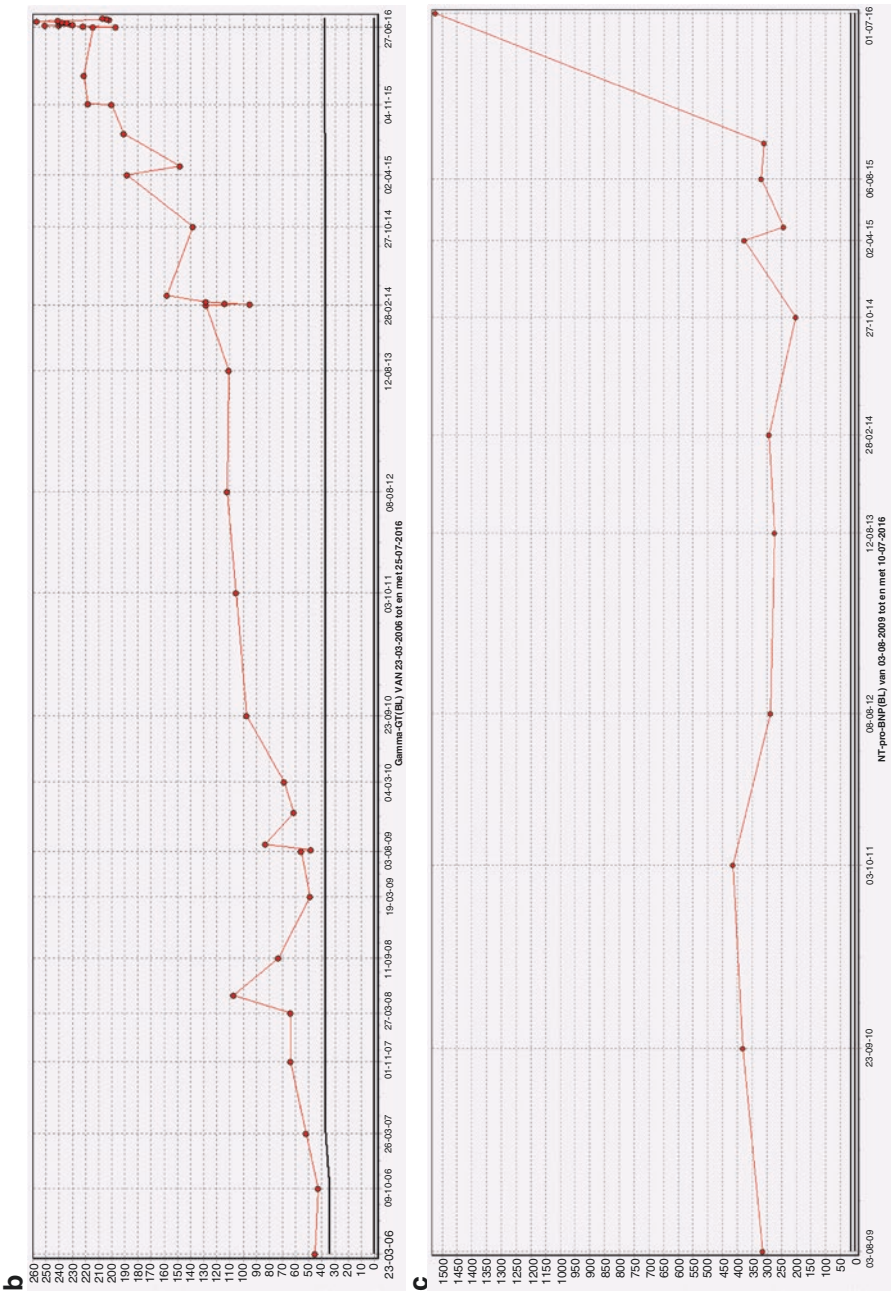

Fig. 3.1 (continued)

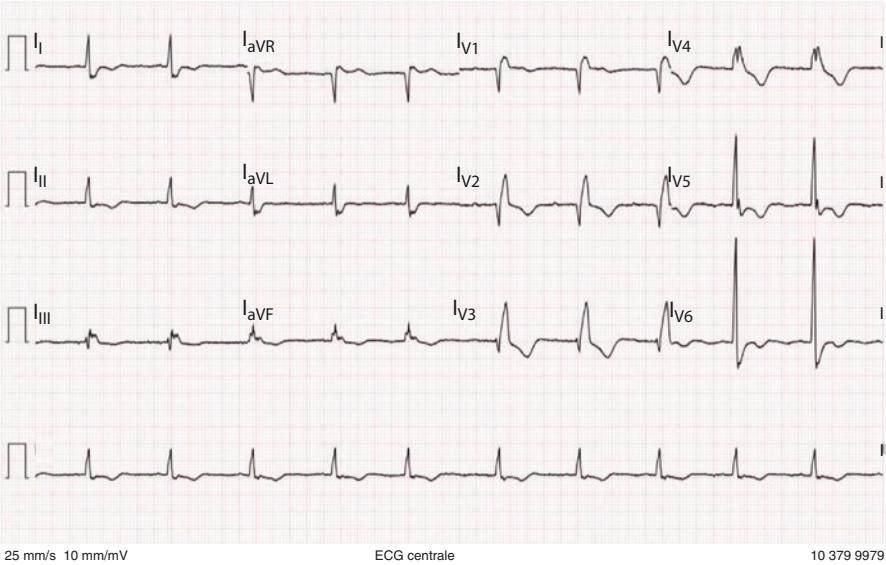

Fig. 3.2 The electrocardiogram of the severe tricuspid regurgitation patient at the last follow-up, showing prominent right bundle branch block with right sided strain pattern, which was present from the very early in the course after the heart transplantation

kidney failure, but she recovered very well. At 3-months follow-up, she was remained stable without signs of herat failure and her renal function was improved to serum creatinine of 125 mmol/L and a e-GFR of 39 mL/min.

Her preoperative (see Fig. 3.3a through c and Videos S1–S3) as well as postoperative (see Fig. 3.3d through f and Videos S4–S6) echocardiographic finding are shown.

Epidemiology

TR prevalance is reported very variable, from 19 to 84% of all HTx recipients [1]. However, in our clinical cohort of 688 patients, severe TR was present in only 32 patients (4.7%), a marked difference, reflecting probably the variable definition used in the literature. In the report by Chan et al. presenting 336 patients, whom were transplanted between 1990 and 1995, they reported moderate TR in 27% and severe in 7%, comparable with our findings [2]. Berger et al. found significant TR in 14.1% of 163 HTx patients between 1988 and 2009, during a mean 8.2 years. Significant TR was correlated with the biatrial surgical technique ($p < 0.01$) and the presence of graft vasculopathy ($p < 0.001$) [3].

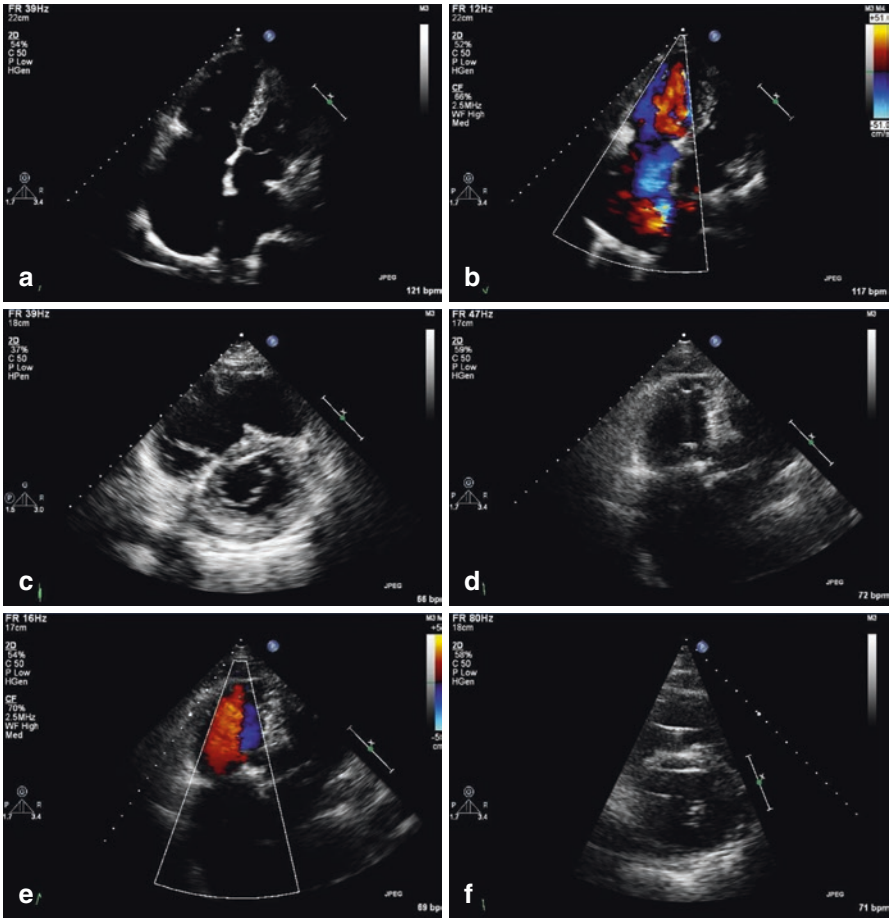

Fig. 3.3 (**a**, **b**, and **c**, Movies S1, S2, and S3) Apical four chamber view demonstrating the severe dilated right ventricle and atrium with severe tricuspid regurgitation. The parasternal short-axis view shows enlarged right ventricle with diastolic collaps ("D-sign") of the interventricular septum. (**d**, **e** and **f**, Movies S4, S5, and S6) Postoperative images, showing relatively reduced right ventricular size, with trace resting tricuspid regurgitation and disappearance of the "D-sign"

Pathophysiology

There are several mechanisms of post HTx TR. Functional TR is usually caused by annular dilation due to postoperative RV failure due to pre-transplant pulmonary hypertension, RV dysfunction after several rejections, or donor-recipient size-mismatch [4]. On the other hand, structural valve abnormalities caused by torn leaflets, ruptured chordae are due to several surveillance EMB's in the first year. The risk of EMB related tricuspid valve damage are related to operator experience, patients clinical state, access site, biotome type [5]. Fiorelli et al. followed 417 HTx patients between 1985 and 2010, who underwent in total 3550 EMB (average 8.5/pt)

after HTx. Traumatic tricuspid valve injury due to EMB rarely leaded to severe valvular regurgitation and only a minority of patients develop significant clinical symptoms [6]. On the other hand, Alharethi et al. found that flail leaflets were the most common operative finding, suggesting that biopsy-induced trauma is the likely cause of severe TI in these patients [7].

In the report by Tarek et al., orthotopic HTx was performed in 249 patients: 161 by the standard technique versus 88 by the bicaval technique. The incidence of both early and late TR was much lower with bicaval technique. Other variables influencing the prevalence of TR was: 2 or more rejections, total number of EMB's and severe preoperative pulmonary hypertension [8]**.** Furthermore, the native and recipient RA diameters were found to be a risk factor for the development of TR. Wartig et al. also found that bicaval orthotopic heart transplantation was the only predictor lower risk of early significant TR (OR = 2.70; 95% CI = 1.68–4.32; $p < 0.001$).

Clinical Features

TR usually remains asymptomatic for years, despite progressive right atrial and ventricular dilatation and right-sided congestion. However, progressive atrial overload and dilatation results in the long-term atrial arrhythmias (atrial tachycardia's and atrial fibrillation). The third phase begins when the heart failure symptoms and signs develop. In this phase, physical examination reveals often markedly pulsating and distended jugular veins, progressive hepatomegaly, pulsating liver ("the liver pulse"), liver enzyme abnormalities, liver fibroses and ultimately cardiac cirrhosis. The classical heart failure biomarker is less reliable in the setting of chronic right sided heart failure as a marker of the progression. As shown in Fig. 3.1, the NT-proBNP is chronically 20–25 times the normal value ($N < 14$) elevated, but escalated very late in the disease course.

If left untreated, symptomatic severe TR results in progressive renal failure, the "cardio-renal syndrome", which is usually accelerated by the need of escalating doses of diuretics.

Management and Prognosis

TR was usually associated with increased mortality and morbidity. Patients with mild or no TR have better survival than those with moderate or severe TR [9]. The optimal treatment of post-transplant severe TR is however not well defined. Since severe TR remains asymptomatic for a long-time it is not unusual that conservative treatment is preferred to surgical treatment. Conservative treatment consist of appropriate management of volume overload and congestion by diuretics. Furthermore, any left sided heart failure and/or pulmonary hypertension should be targeted aggressively. Digoxin should be prescribed for patients who develop signs of right ventricular dysfunction and/or supra-ventricular arrhythmias.

Surgical correction of severe TR is considered as the final solution for patients with refractory right-sided heart failure like in our case [1]. However, the right surgical approach and the timing of the surgery is yet not well defined. Alharethi et al. found that tricuspid valve repair or replacement is a safe and effective procedure to alleviate HF symptoms [7]. They reported data from 17 patients, in which 16 patients tricuspid replacement and in 2 repair was performed. In an another report, eight patients with symptomatic severe TR underwent tricuspid annuloplasty, four had valve repair and annuloplasty, and two had replacement [10]. In three of the six primary repairs failed and required replacement with a bio-prosthesis at 8 days, 14 days and 4 years, respectively. No failure occurred in any of the five bioprosthetic valves placed at a mean 55 months of follow-up.

Bellano et al. followed 96 adult patients who underwent HTx during 2010–2013. Seven patients (7.2%) with severe TVR after median of 47 days (range 27–60) underwent surgical valvular repair. They found that early surgical repair of post-transplant severe TR appears to be a safe treatment strategy in selected patients and is likely to contribute to enhanced cardiac performance and alleviation of associated organ dysfunction [11].

In conclusion, the existing data suggest that the tricuspid valve repair should be considered in patients with dilated tricuspid annulus. On the other hand, bioprosthetic valve replacement is preferred in leaflet prolapse and/or chordal injury.

Key Points

- Tricuspid regurgitation is the most common valvular abnormality after heart transplant.
- The aetiology of post heart transplant is commonly due to tricuspid valvular apparatus damage because of frequent endomyocardial biopsies, annular dilatation due to right heart failure, with or without pre-transplant pulmonary hypertension, and/or distorted tricuspidal anatomy at bi-atrial orthotopic heart transplantation.
- Post heart transplant TR often remain asymptomatic, however in the long-term it is associated with increased mortality and morbidity.
- Surgical valve replacement with a bioprothesis, is warranted in selected cases to prevent progressive renal failure, morbidity and mortality.

Review Questions

Select the Single Best Sentence

24. Which of the following statements about post heart transplantation TR is true?

    (a) TR is in the literature reported very variable, from 19 to 84% of all heart transplant recipients
    (b) TR is reported in 25% in the first postoperative year and is always trace

(c) TR is reported in 25% in the first postoperative year and is always mild
(d) TR is reported in 25% in the first postoperative year and is always severe

25. Which of the following statements about post heart transplantation TR is correct?

(a) Only seen after bicaval but not after biatrial transplantation techniques
(b) Is exclusively seen in patients with patent foramen ovale
(c) Severe TR after heart transplantation is often due to frequent endomyocardial biopsies
(d) Severe TR after heart transplantation is seen in less than 1% of cases

26. Which of the following statements about surgical treatment of post heart transplantation TR is correct?

(a) Flail leaflets are the most common operative finding after heart transplant
(b) Perforated leaflets are the most common operative finding after heart transplant
(c) Restricted leaflets are the most common operative finding after heart transplant
(d) Calcific posterior leaflet is the most common operative finding after heart transplant

27. Which of the following statements about optimal treatment of post heart transplantation TR is correct?

(a) The optimal treatment of post-transplant severe TR is however not well defined
(b) Surgery is indicated for all patients with severe TR regardless symptoms
(c) Catheter based therapy is indicated for all patients with severe TR regardless symptoms
(d) Surgery is indicated for all patients with patients with mild TR when pulmonary hypertension exists

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