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Actual management and prognosis of severe isolated tricuspid regurgitation associated with atrial fibrillation without structural heart disease

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ABSTRACT

Background: Patients with atrial fibrillation (AF) without structural heart diseases can show severe tricuspid regurgitation (TR), especially among aged people. The aim of this study was to clarify the actual management, prognosis, and prognostic factors for severe isolated TR associated with AF without structural heart diseases.
Methods and results: We retrospectively investigated actual management in 178 consecutive patients with severe isolated TR associated with AF between 1999 and 2011 in our institution. Prognosis and its predictors were also investigated in 115 patients (68 persistent TR and 47 transient TR) who were followed-up for >1 year. During the follow-up period (mean: 5.9 years), event free rate from death due to right-sided heart failure (RHF) was 97% at 5 years. Persistent TR was associated with higher risk of hospitalization due to RHF than transient TR (log-rank P = 0.048) and death due to RHF were all seen in patients with persistent TR who experienced hospitalization due to RHF. Among patients with persistent TR, right ventricular outflow tract dimension >35.3 mm, right atrial area >40.3 cm^2, and tenting height >2.1 mm were associated with higher risk of hospitalization due to RHF (adjusted hazard ratio: 3.32, 3.83, and 2.89, respectively; P = 0.003, 0.002, and 0.009, respectively).
Conclusion: The prognosis of severe isolated TR associated with AF was good with a focus on cardiac death. However, the incidence of cardiac death increased among patients who experienced hospitalization due to RHF. Larger right ventricular outflow tract dimension, right atrial area and tenting height were predictors of hospitalization due to RHF.

1. Introduction

Historically, the tricuspid valve was often termed the 'forgotten' valve, as tricuspid regurgitation (TR) is usually a secondary, not primary disease, and right-sided heart failure (RHF) due to TR is usually controllable with diuretic drugs for a prolonged period. More recently, moderate to severe TR was reported to be associated with a poor prognosis [1–4] and TR is now of increasing interest. However, current guidelines propose very limited indications for surgery in patients with isolated secondary (or functional) TR [5,6]. This is partly attributable to a paucity of available data about patients with isolated functional TR compared with left-sided valvular heart disease.

TR commonly occurs as a result of left-sided heart failure and/or pulmonary hypertension. Isolated functional TR without significant left heart failure and/or pulmonary hypertension often occurs in patients with a history of left-sided valve surgery, and there have been many previous studies about isolated TR after left-sided valve surgery [7,8]. On the other hand, patients with AF without structural heart diseases also show severe TR, especially among aged people. Severe TR associated with AF was reported to be strongly related to tricuspid annular dilation, which is similar to isolated functional TR after left-sided valve surgery [9] and the incidence was reported as 7 to 20% among severe TR [10–13]. Although severe TR associated with AF without structural heart diseases is common in clinical settings, there are few reports on

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this disease entity. Thus, the purpose of this study was to clarify the actual management, prognosis, and prognostic factor of severe isolated functional TR associated with AF.

2. Methods

2.1. Study patients

This was a retrospective single-centre cohort study. We retrospectively investigated consecutive transthoracic echocardiographic examinations between 1999 and 2011 in Tenri Hospital and selected patients who showed severe TR. We determined the main aetiology of severe TR based on clinical and echocardiographic findings. Functional TR was defined as regurgitation with apparently anatomically normal leaflets and chordae tendineae. Among patients showing severe TR, primary TR and functional TR due to left-sided valve disease or after left-sided valve surgery, due to left ventricular dysfunction, right ventricular (RV) dysfunction, pulmonary hypertension, or congenital heart disease, and idiopathic TR presenting sinus rhythm were excluded, and we finally selected patients with severe isolated functional TR associated with AF without structural heart disease. We defined this disease group as "idiopathic functional TR with AF".

Left ventricular dysfunction was composed of left ventricular systolic dysfunction and prominent increased wall thickness. Left ventricular systolic dysfunction was defined as <45% left ventricular ejection fraction, and prominent increased wall thickness was defined as ≥13 mm. RV dysfunction was defined as arrhythmogenic right ventricular cardiomyopathy or RV infraction. Pulmonary hypertension was defined as ≥50 mm Hg systolic pulmonary artery pressure, which was calculated from the peak velocity of TR using the Bernoulli equation.

Among patients with idiopathic functional TR with AF, actual status of follow-up and treatment were examined. Furthermore, we investigated prognosis of patients who were followed-up with echocardiography for >1 year and also investigated clinical and echocardiographic characteristics and prognostic predictors in patients who showed persistent severe TR. Informed consent was obtained from all patients. The study protocol was approved by the institutional ethics committee at Tenri Hospital, judging it complaint to the principles outlined in the Helsinki Declaration.

2.2. Clinical features

To investigate the clinical features of patients with idiopathic functional TR with AF, we examined the following factors using previous clinical charts: age, sex, comorbidity, heart rate, and laboratory data at the initial echocardiographic examination showing severe TR. Comorbidity included diabetes mellitus, hypertension, chronic respiratory disease, chronic kidney disease, and chronic liver disorder. Hypertension was defined by a systolic blood pressure of ≥140 mm Hg and/or a diastolic pressure of ≥90 mm Hg, or by the use of antihypertensive medications. Dyslipidaemia was defined by a serum cholesterol level of ≥5.7 mmol/L or the use of cholesterol-lowering medications. Diabetes mellitus was defined as hyperglycaemia requiring medications. Chronic respiratory disease was composed of chronic obstructive pulmonary disease and bronchial asthma. Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 for >3 months. Laboratory data included haemoglobin level, platelet count, estimated glomerular filtration rate, albumin level, and total bilirubin level.

2.3. Echocardiographic parameters

Severe TR was defined as showing a TR jet area of more than 10 cm^2. To investigate the aetiology of TR and the echocardiographic predictors of prognosis, echocardiographic parameters at the initial echocardiographic examination showing severe TR were measured. Echocardiographic parameters included left atrial diameter, left ventricular diastolic diameter, left ventricular ejection fraction, thickness of the interventricular and left ventricular posterior wall, RV outflow tract dimension, RV long axis and short axis dimension, RV spherical index, right atrial area, tricuspid annular diameter, and tenting height of the tricuspid valve.

Conventional parameters such as left atrial diameter, left ventricular diastolic diameter, and thickness of the interventricular and left ventricular posterior wall were measured according to reported guidelines [14]. Left ventricular ejection fraction was measured using the modified Simpson's method. As the right-sided heart parameters were not routinely measured, we re-measured these parameters from the original echocardiographic recordings. The TR jet area was traced from the view where the area was at a maximum. Right-sided heart parameters such as RV outflow tract dimension and right atrial area were measured according to reported guidelines [14]. RV long axis and short axis dimensions at the upper one-third level were measured in the apical 4-chamber view at mid-systole, and RV spherical index was calculated by the ratio of long/short axis [15]. Tricuspid annular diameter was measured in the apical 4-chamber view at end-systole as previously reported [16], while tenting height of the tricuspid valve was measured in the apical 4-chamber view at the mid-systole as the distance from the annular plane to the coaptation point, as previously described [16,17]. Although there are few reports on the normal range of tricuspid annular diameter, we defined tricuspid annular dilatation as tricuspid annular diameter >35 mm, as reported [17].

2.4. Clinical classification of TR

Persistent TR was defined as severe TR which did not improve to less than moderate at follow-up echocardiography with more than a 1-year interval and maintained severe TR. Transient TR was defined as severe TR which improved to less than moderate at follow-up echocardiography with more than a 1-year interval and never became severe subsequently.

2.5. Endpoints

The primary endpoint for this analysis was hospitalization due to RHF. We defined RHF as presenting signs caused by elevated systemic venous pressure, such as leg oedema, congestive liver, and pleural effusion, and requiring intravenous drug treatment. RHF associated with left-sided heart failure was excluded. The secondary endpoints were all cause death, death due to RHF, and tricuspid valve surgery.

2.6. Statistical analysis

Values are expressed as mean ± SD or median and interquartile range for continuous variables, and as numbers and percentages for categorical variables. The difference in a parameter between two groups was determined by unpaired *t*-test or Wilcoxon rank-sum test on the basis of the distribution for continuous variables, and Pearson's Chi-square test for categorical variables. The Kaplan–Meier method was used for estimating cumulative incidence of event free survival and log-rank-test was used to assess differences.

In patients with persistent TR who experienced hospitalization due to RHF, landmark analyses of secondary endpoints were performed. The landmark point was the time of first hospitalization due to RHF.

Then, in patients with persistent TR, receiver operating characteristic analysis and the area under the receiver operating characteristic curves were used to quantify the ability of right-sided echocardiographic parameters to assess the predictor for hospitalization due to RHF and to find the optimal cut-off point of each of the right-sided echocardiographic parameters.

The study patients with persistent TR were dichotomized into two groups according to the cut-off points of each of the right-sided echocardiographic parameters by receiver operating characteristic analysis. The hazard ratio and 95% confidence intervals were calculated using Cox proportional hazard model. We used a multivariate Cox proportional hazard model to assess predictors for hospitalization due to RHF by adjusting for age, haemoglobin levels, and estimated glomerular filtration rate levels, which are well known predictors of prognosis of congestive heart failure [18–20]. Right-sided echocardiographic parameters are intercorrelated with each other, thus different models were performed for a multivariate analyses, including each right-sided echocardiographic parameters, age, haemoglobin levels, and estimated glomerular filtration rate levels.

In addition, in patients without follow-up echocardiography, the Kaplan–Meier method was used and the cumulative incidence of event free survival was calculated. It was not prespecified analyses.

Statistical analysis was performed using JMP version 12. A P value of <0.05 was considered statistically significant.

3. Results

3.1. Aetiology of severe TR and actual management of patients with idiopathic functional TR with AF

We retrospectively investigated 103,648 consecutive transthoracic echocardiographic examinations and selected 1955 examinations from 850 patients who showed severe TR. Of these, we selected 178 patients with idiopathic functional TR with AF. The aetiology of severe TR in the 850 total patients is shown in Table A.1 in Web Appendix. The incidence of idiopathic functional TR with AF was 21%.

Among the 178 patients, follow-up echocardiography with more than a 1-year interval was performed in 115 patients (65%) but no follow-up echocardiography was performed in 63 patients (35%) despite severe TR.

Of these 63 patients without follow-up echocardiography, 7 patients (11%) died shortly after initial echocardiographic examination; all except one died of non-cardiac diseases. Thirty one patients (49%) were transferred to a different hospital for rehabilitation or were referred to a primary physician due to stable medical condition shortly after initial echocardiographic examination, and 25 patients (40%) were followed-up >1 year at our outpatient department, although no follow-up echocardiography was performed. ~~The cumulative survival rate at 5 years was 64%, however the event free rate from death due to RHF at 5 years was 98%.~~

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