ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 2933–2940
Published online 22 July 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12906

ORIGINAL RESEARCH ARTICLE

Characteristics and prognostic implications of tricuspid regurgitation in patients with arrhythmogenic cardiomyopathy

Hyeonju Jeong[1], Shinjeong Song[2], Jiwon Seo[2], Iksung Cho[2], Geu-Ru Hong[2], Jong-Won Ha[2] and Chi Young Shim[2]*

[1]*Division of Cardiology, Myongji Hospital, Hanyang University Medical Center, Goyang, Korea;* [2]*Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea*

Abstract

Aims Arrhythmogenic cardiomyopathy (AC) is characterized by right ventricular (RV) dilatation and dysfunction and is often seen in combination with tricuspid regurgitation (TR). The aim of this study was to investigate the characteristics and prognostic implications of TR in patients with AC.

Methods and results Clinical, echocardiographic, and cardiac magnetic resonance data of 52 patients with AC fulfilling 2010 Task Force criteria in a single centre were retrospectively evaluated. TR in AC was classified as no/mild, moderate, or severe on the basis of the current guidelines. Significant TR was defined as at least moderate TR. The primary endpoint was a composite of death, heart transplantation, and tricuspid valve surgery. There were seven patients (13.4%) with moderate TR and 13 patients (25.0%) with severe TR at initial diagnosis. Patients with severe TR showed a higher prevalence of atrial fibrillation and a higher mean NT-pro-BNP than other groups (68%, $P = 0.013$; 2423 ± 1578 pg/mL, $P < 0.001$, respectively). Patients with significant TR revealed a higher incidence of heart failure at initial presentation than did those without significant TR (30.0 vs. 3.1%, $P = 0.022$). Patients with severe TR showed significantly larger RV and lower RV and left ventricular functional parameters. During a mean follow-up of 4.2 years, three groups classified by TR severity considerably discriminated clinical outcomes (log rank $P = 0.019$). Patients with significant TR had a poorer prognosis than those with no or mild TR (42.9 vs. 3.1%, log rank $P = 0.005$). Cox regression analysis showed significant TR as an independent prognostic factor (hazard ratio 11.41, 95% confidential interval 1.30–99.92, $P = 0.028$).

Conclusions Significant TR at initial diagnosis in patients with AC is a poor prognostic factor.

Keywords Arrhythmogenic cardiomyopathy; Tricuspid regurgitation; Prognosis

Received: 22 July 2019; Revised: 15 June 2020; Accepted: 6 July 2020
**Correspondence to: Chi Young Shim, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea. Tel: +82-2-2228-8453; Fax: +82-2-2227-7742. Email: cysprs@yuhs.ac*

Introduction

Arrhythmogenic cardiomyopathy (AC) is an inherited cardiomyopathy that predominantly affects the right ventricle (RV) and is associated with ventricular arrhythmias, heart failure (HF), and sudden cardiac death.[1,2] RV structural and functional changes in AC may also lead to the development of functional tricuspid regurgitation (TR).[3] Significant TR may contribute to worsened HF by both increased RV filling pressure and lowered RV forward stroke volume.[4]

Severe TR is associated with a poor prognosis independent of age and biventricular systolic function.[5] The prognostic implications of moderate-to-severe TR in mitral valve disease,[6–8] aortic stenosis,[9,10] and chronic HF[11] have been demonstrated. However, the prevalence, characteristics, and prognostic implications of TR in patients with AC are still unclear, although one prior study suggested a potential significance of TR for clinical outcome.[4] Therefore, the aims of this study were to evaluate the prevalence of TR in AC, to define clinical and echocardiographic

characteristics of patients with AC according to TR severity, and to identify the prognostic implications of TR in patients with AC.

Methods

Study population

We retrospectively investigated 52 patients (39 men, mean age 47 ± 19 years) with AC who met the 2010 Revised Task Force Criteria[12] and who were available for follow-up in Severance Cardiovascular Hospital from March 2005 to May 2018. Family history, previous documented ventricular arrhythmias, age, co-morbidities, and clinical presentation at onset were systematically assessed. All patients underwent physical examination, laboratory tests, 12-lead electrocardiogram, and transthoracic echocardiography. Cardiac magnetic resonance imaging or endomyocardial biopsy was performed in selected cases according to physician decisions. Among 52 patients, 41 patients (79%) underwent cardiac magnetic resonance imaging and 15 patients (29%) underwent endomyocardial biopsy at initial diagnosis. The Institutional Review Board of Severance Hospital approved the present study, which was conducted in compliance with the Declaration of Helsinki.

Echocardiography

Standard two-dimensional and Doppler measurements were performed following the American Society of Echocardiography guidelines.[13] TR severity was classified as no/mild, moderate, or severe according to the integration of multiple parameters recommended in current guidelines.[14] Significant TR was defined as moderate or severe TR.

RV systolic dysfunction was defined by two-dimensional echocardiography. RV area measurements were taken from the apical four-chamber focused RV view at end-diastole and end-systole, and RV fractional area change (FAC) was calculated as the ratio between the difference of the end-diastolic and end-systolic RV areas and the end-diastolic area.[13] RV FAC $<$ 33% ($<$2 standard deviations from normal values) defines RV systolic dysfunction, while RV FAC $\leq$ 25% ($\leq$3 standard deviations from normal values) defines severe RV systolic dysfunction.[4] Left ventricular (LV) dysfunction was defined when LV ejection fraction was lower than 50% and/or as the presence of akinesia or dyskinesia.[4] Echocardiographic data were carefully reviewed by two experienced cardiologists who were blinded to clinical data.

Follow-up and outcomes

The primary endpoint was a composite of death, heart transplantation, and tricuspid valve surgery. Additionally, appropriate shock with implantable cardioverter defibrillator (ICD) and hospitalization due to worsened HF were analysed as the second endpoints. Surgical treatments including heart transplantation and tricuspid valve surgery were determined at the discretion of attending physicians. The appropriateness of ICD shocks was judged by an electrophysiologist who reviewed intracardiac electrocardiograms. Worsened HF was defined by signs and symptoms such as dyspnoea, rales, and ankle oedema, as well as the need for diuretic agents, vasodilators, or positive inotropic drugs.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as number (percentage). Comparisons between groups were performed using standard λ^2 tests for categorical variables and paired *t*-tests for continuous variables. Univariate and multivariate logistic regression analyses were performed. Survival curves were constructed using the Kaplan–Meier method, and comparisons were made using the log-rank test. All statistical analyses were performed using SPSS Statistics, software version 25.0 (IBM, Armonk, NY, USA); *P*-values _x0003C; 0.05 were considered statistically significant.

Results

Characteristics of patients with arrhythmogenic right ventricular cardiomyopathy combined with tricuspid regurgitation

Table 1 shows baseline characteristics according to initial TR severity. At the time of diagnosis, seven patients (13.5%) had moderate TR and 13 patients (25.0%) had severe TR by echocardiography. Therefore, moderate-to-severe TR, which was classified as significant TR, was observed in 20 patients (38.5%) with arrhythmogenic right ventricular cardiomyopathy (ARVC).

There were no significant differences in age, sex proportion, and body mass index among the three groups. The incidence of diabetes mellitus and atrial fibrillation was significantly higher in patients with severe TR than in the other groups. However, there were no differences in the prevalence of hypertension and coronary artery disease. On laboratory findings, NT-pro-BNP was significantly greater in the severe TR group than in the other groups despite no differences in renal function or haemoglobin level.

Table 1 Baseline characteristics

	No/mild TR (n = 32)	Moderate TR (n = 7)	Severe TR (n = 13)	P-value
Age, years	44 ± 19	57 ± 14	50 ± 19	0.220
Male, n (%)	25 (78)	5 (71)	9 (69)	0.800
Body mass index, kg/m^2	23.8 ± 3.2	24.3 ± 2.6	24.4 ± 3.3	0.875
Hypertension, n (%)	9 (28)	1 (14)	2 (15)	0.550
Diabetes mellitus, n (%)	1 (3)	1 (14)	5 (38)	0.007
CAD, n (%)	4 (13)	0 (0)	4 (31)	0.147
AF, n (%)	9 (28)	5 (71)	9 (69)*	0.013
Systolic BP, mmHg	115 ± 13	121 ± 13	117 ± 17	0.604
Diastolic BP, mmHg	72 ± 11	72 ± 15	72 ± 15	1.000
Haemoglobin, g/dL	13.8 ± 2.0	14.1 ± 1.7	13.9 ± 2.1	0.921
eGFR, mL/min/1.73 m^2	79.8 ± 18.3	83.3 ± 8.8	82.5 ± 11.3	0.814
NT-pro-BNP, pg/mL	688 ± 741	608 ± 595	2423 ± 1578*,**	<0.001
ICD, n (%)	16 (50)	5 (71)	6 (46)	0.525
Initial presentation				
SCD, n (%)	8 (25)	2 (29)	1 (8)	0.382
VT/VF, n (%)	10 (31)	3 (43)	4 (31)	0.827
Syncope, n (%)	5 (16)	0 (0)	1 (8)	0.444
Heart failure, n (%)	1 (3)	2 (29)*	4 (31)*	0.022
Others, n (%)	8 (25)	0 (0)	3 (23)	0.334

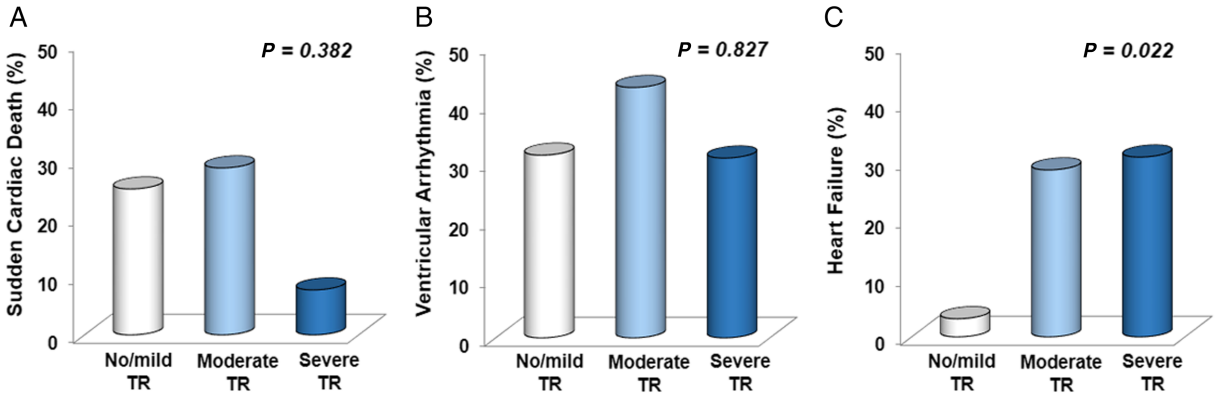
AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; NT-pro-BNP, N-terminal pro brain natriuretic peptide; SCD, sudden cardiac death; TR, tricuspid regurgitation; VF, ventricular fibrillation; VT, ventricular tachycardia.
*$P < 0.05$ compared with no/mild TR group.
**$P < 0.05$ compared with moderate TR group.

In terms of initial clinical presentation of AC, ventricular arrhythmia was the most common in all groups. Sudden cardiac death tended to be more prevalent in patients with no/mild TR or moderate TR than in those with severe TR. Few patients had HF in the no or mild TR group, but it was significantly more common in the moderate and severe TR groups (P = 0.022) (*Figure 1*).

Echocardiographic characteristics are presented in *Table 2*. Severe TR groups showed significantly lower LV ejection fraction than the other groups. Patients with severe TR had a higher E/e′ than patients with no/mild TR. As expected, RV dimensions assessed on parasternal views and RV focused views were significantly larger in the severe TR group than were variables in the other groups. Interestingly, the difference in mid-RV dimension were apparent between patients with moderate TR and those with severe TR. RV functional variables such as FAC, tricuspid annular plane systolic excursion, and S′ velocity at the tricuspid annulus were significantly lower than in other groups. LV dysfunction was prevalent in the severe TR group, but there was no difference in the incidence of RV dysfunction among the three groups.

Cardiac magnetic resonance findings are presented in *Table 3*. The data showed consistent echocardiographic data in terms of chamber size and function. The RV dimension and volume were larger in the severe TR group, and the LV and RV ejection fractions were lower. However, there was no significant difference between the three groups in myocardial tissue characteristics such as late gadolinium enhancement and fat deposition.

FIGURE 1 Initial clinical presentations of patients with arrhythmogenic cardiomyopathy (AC) according to tricuspid regurgitation (TR) severity. (A) Sudden cardiac death. (B) Ventricular arrhythmia. (C) Heart failure.



DOI: 10.1002/ehf2.12906

Table 2 Echocardiographic characteristics

	No/mild TR (n = 32)	Moderate TR (n = 7)	Severe TR (n = 13)	P-value
Characteristics of left chambers				
LV EDD, mm	50.0 ± 5.1	46.9 ± 6.2	48.7 ± 5.9	0.345
LV ESD, mm	35.8 ± 6.3	32.6 ± 6.0	38.4 ± 7.9	0.181
LV EF, %	56.8 ± 11.5	64.0 ± 7.6	43.1 ± 16.2*,**	0.001
LV mass index, g/m^2	87.3 ± 24.6	88.8 ± 23.9	88.5 ± 28.0	0.984
LA volume index, mL/m^2	27.0 ± 11.8	36.4 ± 12.2	30.5 ± 18.7	0.253
E/e′	11.1 ± 6.1	13.4 ± 7.2	16.5 ± 7.5*	0.135
Characteristics of right chambers				
RVOTd (PLAX), mm	33.2 ± 6.6	36.4 ± 9.1	49.9 ± 13.8*,**	<0.001
RVOTd (PSAX), mm	32.5 ± 7.0	35.1 ± 8.3	45.5 ± 12.5*,**	<0.001
RV EDA, mm^2	27.6 ± 6.0	29.9 ± 11.2	31.0 ± 9.9*	<0.001
RV ESA, mm^2	19.6 ± 5.4	20.9 ± 10.1	31.3 ± 11.7*	<0.001
Basal RV, mm	36.2 ± 5.3	38.9 ± 5.4	43.4 ± 7.9*	0.003
Mid-RV, mm	40.0 ± 7.4	42.6 ± 10.3	54.8 ± 11.7*,**	<0.001
RV length, mm	80.5 ± 8.1	81.1 ± 13.9	86.2 ± 9.3	0.179
FAC, %	29.3 ± 9.6	26.7 ± 12.9	22.9 ± 8.6*	0.147
TAPSE, mm	17.7 ± 5.9	22.8 ± 5.1	11.5 ± 1.9*,**	0.001
S′ velocity, cm/s	9.9 ± 3.2	12.0 ± 2.8	7.4 ± 1.6*,**	0.004
RA area, mm^2	16.2 ± 4.8	22.4 ± 6.8	35.1 ± 19.0*,**	<0.001
TV annulus, mm	33.6 ± 5.2	41.2 ± 18.2*	43.6 ± 8.5*	0.003
TR VCW, mm	3.0 ± 1.3	4.7 ± 0.5*	10.8 ± 4.6*,**	<0.001
TR velocity, m/s	2.2 ± 0.2	2.6 ± 0.5	2.0 ± 0.4*,**	0.001
RVSP, mmHg	26.6 ± 5.5	37.7 ± 15.3*	31.9 ± 5.9*	0.002
Ventricular dysfunction				
LV dysfunction, n (%)	7 (22)	0 (0)	7 (54)*	0.020
RV dysfunction, n (%)	19 (59)	4 (57)	10 (77)	0.505
Both, n (%)	7 (22)	0 (0)	5 (39)	0.145

E/e′, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity; e′, early diastolic mitral annular tissue; EDA, end-diastolic area; EDD, end-diastolic dimension; EF, ejection fraction; ESA, end-diastolic area; ESD, end-systolic dimension; FAC, fractional area change; LAVI, left atrial volume index; LV, left ventricular; RA, right atrium; RV, right ventricular; RVOTd (PLAX), right ventricular outflow track diameter at parasternal long axis view; RVOTd (PSAX), right ventricular outflow track diameter at parasternal short axis view; RVSP, right ventricular systolic pressure; S′, tricuspid annulus systolic tissue; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV, tricuspid valve; VCW, vena contracta width.
*$P < 0.05$ compared with no or mild TR group.
**$P < 0.05$ compared with moderate TR group.

Table 3 Cardiac magnetic resonance findings

	No/mild TR (n = 27)	Moderate TR (n = 5)	Severe TR (n = 9)	P-value
LV EDV, mL	176 ± 47	143 ± 37	154 ± 51	0.250
LV ESV, mL	85 ± 41	64 ± 31	85 ± 45	0.559
LV EF, %	53 ± 11	58 ± 11	43 ± 22	0.133
LV LGE, n (%)	6 (22)	3 (60)	4 (44)	0.325
RV EDV, mL	227 ± 51	203 ± 115	357 ± 134*,**	0.001
RV ESV, mL	136 ± 46	108 ± 73	292 ± 146*,**	<0.001
RV EF, %	41 ± 12	50 ± 9	23 ± 11*,**	0.001
RV LGE, n (%)	14 (52)	3 (60)	8 (89)	0.353
Fat deposition, n (%)	6 (22)	0 (0)	1 (11)	0.762

EDV, end-diastolic volume; ESV, end-systolic volume; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; TR, tricuspid regurgitation.
*$P < 0.05$ compared with no or mild TR group.
**$P < 0.05$ compared with moderate TR group.

Clinical outcomes according to tricuspid regurgitation severity in arrhythmogenic right ventricular cardiomyopathy

Clinical outcomes are shown in *Table 4*. There were significantly more heart transplantation and tricuspid valve surgeries in the severe TR group than in other groups. The composite of death, HT, and tricuspid valve surgery was significantly more prevalent in the severe TR group than the other groups. However, secondary endpoints such as appropriate ICD shock and hospitalization due to worsened HF were not significantly different between subgroups. Survival analysis was performed on the composite of death, heart transplantation, and tricuspid valve surgery during the

Table 4 Clinical outcomes

	No/mild TR (n = 32)	Moderate TR (n = 7)	Severe TR (n = 13)	P-value
Primary endpoints				
Death	1 (3.1)	1 (14.3)	1 (7.7)	0.488
Heart transplantation	0 (0.0)	0 (0.0)	4 (30.8)*	0.002
Tricuspid valve surgery	0 (0.0)	1 (14.3)*	2 (15.4)*	0.078
Secondary endpoints				
Appropriate shock of ICD	13 (40.6)	3 (42.9)	3 (23.1)	0.505
Hospitalization due to worsened HF	8 (25.0)	3 (42.9)	5 (38.5)	0.511

HF, heart failure; ICD, implantable cardioverter defibrillator; TR, tricuspid regurgitation.
*$P < 0.05$ compared with no or mild TR group.

FIGURE 2 Kaplan–Meier analysis of freedom from primary endpoints. (A) Comparison in three groups classified by tricuspid regurgitation (TR) severity. (B). Comparison in two groups according to presence of significant TR.

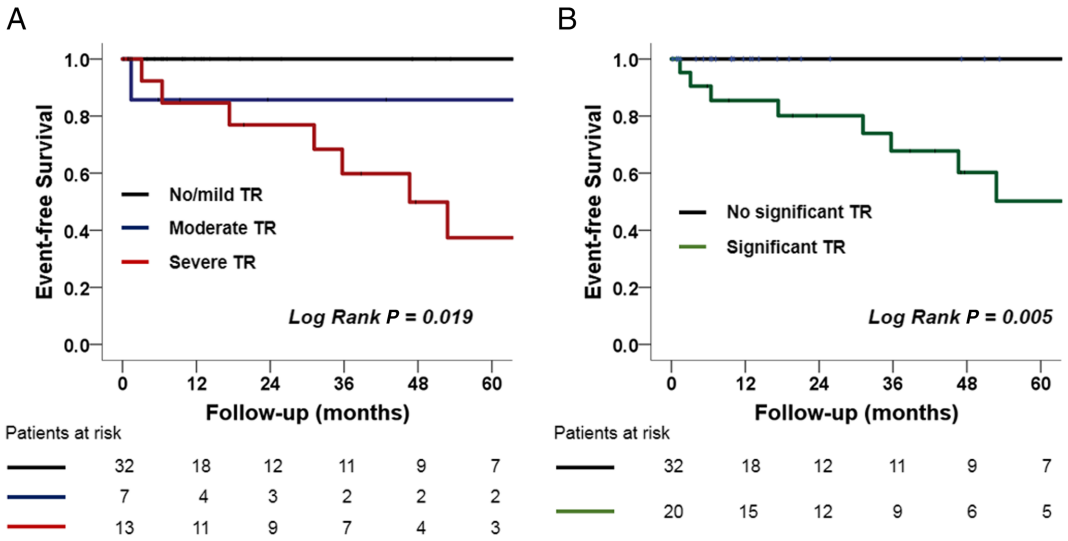


Table 5 Cox proportional regression analysis for primary endpoints

	Univariate			Multivariate		
Primary endpoints	HR	95% CI	P-value	HR	95% CI	P-value
Age	0.99	0.95–1.03	0.532	0.99	0.94–1.04	0.649
Female sex	0.96	0.20–4.67	0.963	0.86	0.11–6.66	0.884
Diabetes mellitus	0.77	0.16–3.79	0.743	0.07	0.00–1.43	0.084
AF	2.78	0.57–13.52	0.206	5.52	0.95–31.89	0.057
LV dysfunction	1.84	0.51–6.68	0.351	3.25	0.45–23.46	0.243
Severe RV dysfunction	2.71	0.69–10.61	0.151	3.87	0.59–25.34	0.158
Significant TR	9.61	1.21–76.16	0.032	11.41	1.30–99.92	0.028

AF, atrial fibrillation; CI, confidential interval; HR, hazard ratio; LV, left ventricular; RV, right ventricular; TR, tricuspid regurgitation.

mean follow-up duration of 4.2 years. The severe TR group had significantly lower event-free survival than other groups (log rank P = 0.019, *Figure 2A*). When divided into significant TR group or not, the significant TR group also showed significantly lower event-free survival than the not significant TR group (log rank P = 0.005, *Figure 2B*). Cox regression analysis showed that significant TR was an independent prognostic factor after controlling for age at diagnosis, sex, presence of diabetes mellitus, atrial fibrillation, LV dysfunction, and severe RV dysfunction (hazard ratio 11.41, 95% confidential interval 1.30–99.92, P = 0.028) (*Table 5*).

Discussion

The principal findings of this study are that (i) the prevalence of significant TR at initial diagnosis was not uncommon in patients with AC; (ii) patients with significant TR showed worse clinical outcome than those without; and (iii) presence of significant TR was an independent prognostic factor after controlling age, sex, atrial fibrillation, and LV or RV dysfunction. These results suggest that patients with AC require careful follow-up to assess TR because TR severity provides prognostic information in this specific population.

In this study, the prevalence of significant TR, defined as moderate or severe TR, was 38.5%. The prevalence of TR in ARVC has been shown at varying levels in previous studies. In a multicentre cohort of 96 AC patients, significant TR was 15% in the overall population.[4] The higher prevalence of significant TR in our study might be explained by some differences in baseline characteristics and definition of significant TR. Our study population was older and tended to have more co-morbidities than the previous cohort population. A previous study also reported the prevalence of significant TR as 14% in 70 patients with AC.[15] Compared with this previous study, our study population showed more advanced RV remodelling and functional impairment, which may influence the higher prevalence of significant TR.

TR that occurs despite structurally normal leaflets is termed functional TR. Because AC is characterized by RV dilatation and dysfunction, significant functional TR can be expected in a considerable number of patients in the course of AC disease progression. In a previous study regarding the mechanisms of functional TR, RV remodelling patterns are not uniform.[16] Idiopathic functional TR associated with aging or atrial fibrillation showed wider RV base and annulus, while functional TR with pulmonary hypertension revealed only modest annular dilatation with leaflet tethering above the annular level and RV lengthening.[16] In the present study, AC patients with severe TR demonstrated modest annular and basal RV dilatation but significantly wider mid-RV dimension and RV outflow tract diameters than did the other groups. However, the RV length in three groups was not different. RV morphologic changes in AC frequently occur at the inferior-sub-tricuspid and mid-RV outflow track.[3] As the disease progresses, global RV dilatation and dysfunction often lead to the development of functional TR without pulmonary hypertension.[3]

In our study, patients with severe TR showed higher NT-proBNP and HF manifestations. Interestingly, patients with moderate TR also presented with a higher incidence of HF at initial presentation. Even in patients with clinically significant TR, TR is often asymptomatic. Theoretically, lesser degrees of TR could have adverse hemodynamic effects because the RV is already damaged in patients with AC. Therefore, the presence of moderate TR combined with RV dysfunction may contribute to the HF and poor clinical outcomes of this study.

TR is an important prognostic factor in various diseases. Neuhold *et al.*[11] studied the impact of moderate and severe TR for endpoints such as death, heart transplantation, and LV assist device implantation in 576 patients with HF. TR was significantly associated with poor outcomes in patients with mild or moderate LV dysfunction. TR has been suggested as a predictive factor of survival, HF, and functional capacity in patients with mitral valve disease.[17] It has been reported that when RV dysfunction had already progressed, the prognosis was poor even if TR was corrected. Thus, TR is associated with poor prognosis in various cardiac conditions, especially if it is combined with ventricular dysfunction. However, there are scant data regarding TR in AC. This is a meaningful study showing the prognostic implications of significant TR by focusing on TR in AC. Previous studies have more focused on arrhythmic risks or myocardial function in specific cardiomyopathies.[2] Several studies have shown that patients with more extensive RV and/or LV disease have a higher arrhythmic risk and poor clinical outcomes.[4,15,18] In a 10 year registry study, significant TR was shown to be an independent predictor for cardiac death or heart transplantation.[4] Furthermore, recent studies suggested clinical implications of atrial arrhythmias in patients with AC not only for inappropriate ICD shocks but also for increased risk of HF and death.[19,20] TR may initiate a cycle that propagates further dilatation and dysfunction in both the RV and right atrium, which induces atrial arrhythmia and worsening TR.

The results of this study have several clinical implications. First, patients with significant TR at initial diagnosis of AC should be carefully treated with medication, rehabilitation, and lifestyle modification to improve clinical outcomes. Second, comprehensive echocardiographic follow-up should focus on both RV function and changes in TR severity to optimally time heart transplantation or intervention for significant TR. In this study, three patients underwent tricuspid valve surgery. However, surgical correction of significant TR is particularly challenging because of the higher risks of postoperative HF and arrhythmic events. In the near future, transcatheter intervention to reduce TR severity may be applied in patients with AC.

Limitations

First, this was a single-centre retrospective study in a tertiary referral centre. Therefore, the prevalence of significant TR observed in this study might be overestimated because of a higher proportion of patients with advanced AC in a spectrum of the disease. Although dynamic changes in TR severity during the follow-up might affect the clinical course, the present study did not include the longitudinal echocardiographic data. Second, this study was limited to Korean patients with AC. To interpret and apply the main results to all races, further studies in another population are warranted. However,

we believe that our study is meaningful because most data for patients with AC have originated only from Caucasian populations. Third, genetic mutations were not studied in this population. Because a recent study demonstrated a potential association between desmoglein-2 mutation carriers and end-stage HF,[21] further genetic studies about HF and TR are warranted.

Conclusions

TR is common in patients with AC. Because echocardiographic evaluation of TR severity in patients with AC provides prognostic information, the presence of significant TR in patients with AC should be closely monitored.

Clinical perspective

Arrhythmogenic cardiomyopathy is an inherited cardiomyopathy that predominantly affects the RV. RV structural and functional changes in AC may also lead to the development of functional TR. Significant TR may contribute to worsened HF by both increased RV filling pressure and lowered RV forward stroke volume. In this study, we found that the prevalence of significant TR at initial diagnosis was not uncommon in patients with AC. This study added important data on the prognostic value of significant TR in patients with AC. It may be suggested that patients with AC require careful follow-up to assess TR because TR severity provides prognostic information in this specific population.

Acknowledgement

None.

Conflict of interest

None declared.

References

1. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med* 2017; **376**: 61–72.
2. Calkins H, Corrando D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2017; **136**: 2068–2082.
3. Katritsis G, Shah AS, James CA, Murray B, Tichnell C, Judge DP, Calkins H, Tedford RJ. Surgical correction of tricuspid regurgitation in patients with ARVD/C. *Heart Rhythm Case Rep* 2015; **1**: 326–330.
4. Pinamonti B, Dragos AM, Pyxaras SA, Merlo M, Pivetta A, Barbati G, Di Lenarda A, Morgera T, Mestroni L, Sinagra G. Prognostic predictors in arrhythmogenic right ventricular cardiomyopathy: results from a 10-year registry. *Eur Heart J* 2011; **32**: 1105–1113.
5. Nath J, Foster E, Hidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004; **43**: 405–409.
6. Boyaci A, Gokce V, Topaloglu S, Korkmaz S, Goksel S. Outcome of significant functional tricuspid regurgitation late after mitral valve replacement for predominant rheumatic mitral stenosis. *Angiology* 2007; **58**: 336–342.
7. Ruel M, Rubens FD, Masters RG, Pipe AL, Bédard P, Mesana TG. Late incidence and predictors of persistent or recurrent heart failure in patients with mitral prosthetic valves. *J Thorac Cardiovasc Surg* 2004; **128**: 278–283.
8. Sagie A, Schwammenthal E, Newell JB, Harrell L, Joziatis TB, Weyman AE, Levine RA, Palacios IF. Significant tricuspid regurgitation is a marker for adverse outcome in patients undergoing percutaneous balloon mitral valvuloplasty. *J Am Coll Cardiol* 1994; **24**: 696–702.
9. Amano M, Izumi C, Taniguchi T, Morimoto T, Miyake M, Nishimura S, Kitai T, Kato T, Kadota K, Ando K, Furukawa Y, Inada T, Inoko M, Ishii K, Sakaguchi G, Yamazaki F, Koyama T, Komiya T, Yamanaka K, Nishiwaki N, Kanemitsu N, Saga T, Ogawa T, Nakayama S, Tsuneyoshi H, Iwakura A, Shiraga K, Hanyu M, Ohno N, Fukumoto A, Yamada T, Nishizawa J, Esaki J, Minatoya K, Nakagawa Y, Kimura T. Impact of concomitant tricuspid regurgitation on long-term outcomes in severe aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2019; **20**: 353–360.
10. Lindman BR, Maniar HS, Jaber WA, Lerakis S, Mack MJ, Suri RM, Thourani VH, Babaliaros V, Kereiakes DJ, Whisenant B, Miller DC, Tuzcu EM, Svensson LG, Xu K, Doshi D, Leon MB, Zajarias A. Effect of tricuspid regurgitation and the right heart on survival after transcatheter aortic valve replacement: insight from the placement of aortic transcatheter valves II inoperable cohort. *Circ Cardiovasc Interv* 2015; **8**: e002073.
11. Neuhold S, Huelsmann M, Pernicka E, Graf A, Bonderman D, Adlbrecht C, Binder T, Maurer G, Pacher R, Mascherbauer J. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. *Eur Heart J* 2013; **34**: 844–852.
12. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J* 2010; **31**: 806–814.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28**: 1–39.e14.
14. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Shernan S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the

American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017; **30**: 303–371.
15. Saguner AM, Vecchiati A, Baldinger SH, Rüeger S, Medeiros-Domingo A, Mueller-Burri AS, Haegeli LM, Biaggi P, Manka R, Lüscher TF, Fontaine G, Delacrétaz E, Jenni R, Held L, Brunckhorst C, Duru F, Tanner FC. Different prognostic value of functional right ventricular parameters in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circ Cardiovasc Imaging* 2014; **7**: 230–239.
16. Topilsky Y, Khanna A, Le Tourneau T, Park S, Michelena H, Suri R, Mahoney DW, Enriquez-Sarano M. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. *Circ Cardiovasc Imaging* 2012; **5**: 314–315.
17. Shiran A, Sagie A. Tricuspid regurgitation in mitral valve disease incidence, prognostic implications, mechanism, and management. *J Am Coll Cardiol* 2009; **53**: 401–408.
18. Mast TP, Teske AJ, vd Heijden JF, Groeneweg JA, Te Riele AS, Velthuis BK, Hauer RN, Doevendans PA, Cramer MJ. Left ventricular involvement in arrhythmogenic right ventricular dysplasia/cardiomyopathy assessed by echocardiography predicts adverse clinical outcome. *J Am Soc Echocardiogr* 2015; **28**: 1103–1113 e9.
19. Camm CF, James CA, Tichnell C, Murray B, Bhonsale A, te Riele AS, Judge DP, Tandri H, Calkins H. Prevalence of atrial arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Heart Rhythm* 2013; **10**: 1661–1668.
20. Zghaib T, Bourfiss M, van der Heijden JF, Loh P, Hauer RN, Tandri H, Calkins H, Nazarian S, Te Riele ASJM, Zimmerman SL, Velthuis BK. Atrial dysfunction in arrhythmogenic right ventricular cardiomyopathy. *Circ Cardiovasc Imaging* 2018; **11**: e007344.
21. Hermida A, Fressart V, Hidden-Lucet F, Donal E, Probst V, Deharo JC, Chevalier P, Klug D, Mansencal N, Delacretaz E, Cosnay P, Scanu P, Extramiana F, Keller DI, Rouanet S, Charron P, Gandjbakhch E. High risk of heart failure associated with desmoglein-2 mutations compared to plakophilin-2 mutations in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Eur J Heart Fail* 2019; **21**: 792–800.