Significant tricuspid regurgitation in patients with arrhythmogenic right ventricular cardiomyopathy

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heritable disorder characterized by fibrofatty replacement of the myocardium. [(1)] These changes can ultimately lead to remodeling of the right ventricle (RV) and tricuspid annular dilatation resulting in a significant secondary tricuspid regurgitation (TR) which could further worsen the RV function in a vicious cycle.[(2)] Prior studies showed that TR is an independent predictor of disease progression in ARVC patients.[(3)] In this study, we hypothesized that decongestive therapy for significant TR (medical and/or surgical intervention) may prevent or slow progression of TR and improve symptoms.

This is a retrospective review of a prospectively enrolled registry of a single-center study conducted at the University of California, San Francisco (UCSF) . All patients were diagnosed with definite ARVC per the 2010 Revised Task Force Criteria at our institution and prospectively enrolled into the UCSF-ARVC registry. All gave informed written consent as approved by the institutional review board. Patients were followed periodically with clinic visits as clinically indicated includes serial electrocardiograms, transthoracic echocardiograms (TTE), and defibrillator device interrogations. Patients enrolled in the registry with symptomatic significant TR, defined as moderate or severe TR per standard definition and current guidelines[(2)] with at least New York Heart Association symptom (NYHA) class II, were retrospectively included in the study.

Per standard care at our institution, symptomatic patients with significant TR were offered decongestive therapy which included preload reduction/diuretics (eg. isosorbide dinitrate, loop diuretics) and afterload reduction (eg. mineralocorticoid receptor antagonist, hydrochlorothiazide, renin-angiotensin-aldosterone system blocker). Patients with NYHA class III or higher and persistent significant TR despite medical treatment were referred for

considerations of tricuspid valve intervention and/or heart transplantation evaluation when deemed appropriate. All patients had an index TTE showing significant TR and had follow-up TTE as clinically indicated. Initial decongestive therapy (mean daily doses or equivalent) of the included patients were, titrated as tolerated, isosorbide mononitrate (30 mg), furosemide (82 mg), spironolactone (50 mg), sacubitril/valsartan (42.25/45.25 mg), hydrochlorothiazide (25 mg). Other cardiac medications included metoprolol (65 mg) and sotalol (176 mg). The follow-up duration was defined by the date of first echocardiogram that made the diagnosis of significant TR and the latest echocardiogram report. During follow-up, patients were classified as 1) responders; defined by symptoms improvement or stabilization by maintaining on the same or minimally-adjusted medical therapy, or 2) non-responders; defined as worsening symptoms, need for escalation of medical therapy, need for intervention (intervention for tricuspid valve or advanced heart failure therapy), or death.

The UCSF-ARVC registry comprised 49 patients with definite ARVC, 10 of whom had symptomatic significant TR. The mean age was 54.7 ± 9.7 years, 5 (50%) were female, and 4 (40%) had pathogenic PKP2 mutation. All had preserved left ventricular ejection fraction (LVEF) (mean 60±9%) and at least moderate RV dysfunction and dilatation. All had history of ventricular arrhythmias and underwent defibrillator implantation. Atrial fibrillation was presented in 4 (40%) patients. One patient had a defibrillator lead entrapped in the tricuspid valve and likely contributing to the significant TR. No evidence of lead entrapment of lead restricting tricuspid valve movement in other 9 patients. During a follow-up period of 3.1 ± 2.3 years (from the index TTE showing significant TR to the last available TTE or outcomes), 4 (40%) patients were responders, and 6 (60%) patients were non-responders. Among the non-responders, 2 patients died, and 4 patients underwent heart transplant, including 1 patient who

did not have symptoms improvement following surgical tricuspid valve repair (**Figure**). The symptoms and clinical of the patient with lead entrapment stabilized with medical therapy and the patient did not undergo lead extraction. Follow-up echocardiogram was available in 9 patients (1 died before repeat echocardiogram). The responders (n=4) all had improvement in TR severity and had significantly more pronounced increase in tricuspid annular plane systolic excursion (TAPSE) (0.59 cm vs 0.06 cm, p = 0.035) and trend toward more reduction in RV basal diameter (-0.6 cm vs +0.7 cm, p = 0.068) than the non-responders (n=5) on follow-up echocardiogram. There were no differences in changes in RV S' velocity (1.8 cm/s vs 1.1 cm/s, p = 0.86) or any of the changes in LV dimensions (including LVEF, end systolic volume and diameter, end diastolic volume and diameter) between the two groups.

To the best of our knowledge, this is the first study in humans that describes the effects of decongestive therapy, involving primary therapy to decrease preload and if necessary, included afterload reduction (sacubitril/valsartan)[(4)], aimed to reverse TR severity in patients with definite ARVC. We found that medical therapy for decongestion in significant TR can improve or stabilize symptoms, TR severity, and heart failure status. Those who did not respond to medical therapy, despite having normal left ventricle, had worse outcomes, including need for tricuspid valve intervention, heart transplantation, and death. Improvement of TAPSE and RV basal diameter are associated with better outcome in this population. While this could be due to inadequate statistical power, the significant improvement in TAPSE among responders, rather than S' velocity, underscores the functional recovery of the RV and that longitudinal systolic function may be more sensitive to therapy than tissue Doppler velocities in this cohort

Prior studies showed that significant TR is an independent predictor of disease progression in ARVC patient.[3,4] The significant TR can directly contribute to worse outcome (eg,

right heart failure, venous congestion, arrhythmias), or may simply be a marker of severe and advanced stage of disease, or both. Surgical correction or catheter-based intervention for significant TR has been explored, with some studies suggesting potential improvements in heart failure symptoms.[5] However, the role of medical therapy in managing TR specifically in ARVC patients has not been well-established.

Overall, our findings provide preliminary evidence that the decongestive therapy can stabilize or improve functional status in patients with ARVC with severe TR. Moreover, failure to respond to medical therapy was associated with death or need for heart transplant. Our study is limited by small sample size from single center, lack of control group and retrospective nature of the study, and lack of magnetic resonance imaging data. Further large-scale prospective studies are needed to validate this finding.

Figure legend

Figure: Central illustration. Patients with ARVC with New York Heart Association symptoms class II or higher with significant TR underwent decongestive therapy. Four (40%) patients were responders, and 6 (60%) patients were non-responders. There were no differences in baseline echocardiogram parameters between responders and non-responders. At follow-up transthoracic echocardiogram, the responders (n=4) all had improvement in TR severity and had significantly more pronounced increase in TAPSE (0.59 cm vs 0.06 cm, p = 0.035) and trend toward more reduction in RV basal diameter (-0.6 cm vs +0.7 cm, p = 0.068) than the non-responders (n=5). ARVC: Arrhythmogenic right ventricular dysplasia, ICD: Implantable cardioverter defibrillator, LVEF: Left ventricular ejection fraction, MD: Mean difference, RV: Right ventricle, TAPSE: Tricuspid annular plane systolic excursion, VT: Ventricular tachycardia

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