Surgical correction of tricuspid regurgitation in patients with ARVD/C

George Katritsis, BSc, MB ChB,† Ashish S. Shah, MD, ‡ Cynthia A. James, PhD, * Brittney Murray, MS, * Crystal Tichnell, MGC,† Daniel P. Judge, MD, * Hugh Calkins, MD, FHRS, * Ryan J. Tedford, MD

From the †The ARVD/C Program, The Johns Hopkins Hospital, Baltimore, Maryland, ‡The John Radcliffe Hospital, Nuffield Department of Medicine, Oxford University Hospital, Oxford, United Kingdom, and ‡Department of Cardiac Surgery, The Johns Hopkins Hospital, Baltimore, Maryland.

Introduction

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a genetically determined cardiomyopathy characterized by fibrofatty replacement of predominantly right ventricular (RV) myocardium. Morphologic changes frequently occur at the inferior-subtricuspid and mid-RV outflow tract, and may involve the anteroparial region in severe cases (triangle of dysplasia).

As disease progresses, global RV dilation and RV dysfunction may occur. RV structural changes may also lead to development of functional tricuspid regurgitation (TR), often in the absence of pressure overload from the pulmonary vasculature (eg, pulmonary hypertension or left heart failure). Therefore, TR in the context of ARVD/C may represent a unique phenotype of patients with functional TR. Because RV volume overload from significant TR may in turn worsen RV function, surgical correction of TR could have therapeutic benefit. Both significant TR and RV dysfunction have been independently associated with worse prognosis in ARVD/C. In order to better understand the potential role of surgery in these patients, we reviewed our ARVD/C database to identify patients who underwent surgical correction of TR.

Case series

The Johns Hopkins ARVD Program maintains a research registry of over 1000 ARVD/C patients, patients’ family members, and those with borderline phenotypes. Patients are followed at yearly intervals. We searched the program registry for patients with a definite diagnosis of ARVD/C according to the 2010 Task Force Criteria (n = 321) who underwent surgical treatment for TR and found 3 such patients (Table 1). All underwent genetic testing for ARVD/C, and at minimum were screened for desmoplakin, plakophilin 2, plakoglobin, desmoglein 2, and desmocollin gene mutations. One patient was found to have a pathogenic mutation (case 3). All identified subjects (or their surrogate) gave written informed consent to participate in the study, which was approved by our Institutional Review Board.

Case 1

Tricuspid valve replacement for severe tricuspid regurgitation and stage D, NYHA class IV biventricular failure.

A 66-year-old male subject with previously established ARVD/C and heart failure necessitating multiple hospitalizations over the preceding 15 years presented with progressive dyspnea, worsening fluid retention, abdominal distension, and congestive hepatopathy. He was able to walk only with the help of a cane. He had NYHA class IV symptoms but denied significant left-sided heart failure symptoms including orthopnea or paroxysmal nocturnal dyspnea. He had been turned down for heart transplantation at 3 different centers owing to a combination of suspected liver disease and amiodarone-induced lung disease. In addition to heart failure, his ARVD/C course was remarkable for significant atrial and ventricular arrhythmias, requiring multiple ablation attempts, antiarrhythmic therapy, and implantation of a cardiac resynchronization therapy defibrillator device.

Transesophageal echocardiography (TEE) showed severe right atrial (RA) and RV dilation (RV internal diameter 8.1 cm), with severe global hypokinesis of the right ventricle. There was septal flattening consistent with RV volume...
overload and severe TR (right ventricular systolic pressure [RVSP] 31 mm Hg). Left ventricular ejection fraction (LVEF) was 30%–40%. Preoperative right heart catheterization showed an RA pressure of 15 mm Hg, normal pulmonary vascular resistance (1.8 Wood units), and a low right ventricular stroke work index of 1.8 g * m/m². Left-sided filling pressures were borderline (pulmonary capillary wedge pressure of 15 mm Hg).

Given his lack of other clinical options and significant symptoms, he was referred for high-risk tricuspid valve (TV) repair/replacement. Intraoperative transesophageal echocardiography (TEE) showed that the TV annulus was severely dilated (5.2 cm), with tethering of the anterior TV leaflet. A downsizing annuloplasty was performed and a 30 mm Edwards MC3 ring was initially seated. Because tethering of the anterior TV leaflet was still apparent, the annuloplasty ring was removed and the annulus downsized further with sutures, before a 31 mm Medtronic Mosaic annuloplasty ring was removed and the annulus downsized (Reed) was performed. At this point, an intraoperative TEE still demonstrated moderate TR and chordal shortening of the anterior TV leaflet. Moderate TR persisted intraoperatively and therefore a modified Duran ring TV valvuloplasty was performed with closure of an accessory commissure of the anterior leaflet. Moderate TR persisted postoperatively and therefore a modified De Vega annuloplasty (Reed) was performed. At this point, an intraoperative TEE still demonstrated moderate TR and chordal lengthening of the anterior TV leaflet was accomplished. The

A 68-year-old male subject with a 12-year history of right heart failure presented with a history of progressive dyspnea on exertion, fatigue, and worsening lower extremity edema consistent with NYHA class III limitations. His medical history was also remarkable for chronic atrial fibrillation and exercise-induced ventricular tachycardia (VT). TTE showed severe RA and isolated RV dilation with moderate to severe RV global systolic hypokinesis. Severe TR was present with a normal RVSP (27 mm Hg). There was paradoxic septal motion consistent with volume overload. Additionally, mild mitral regurgitation associated with mitral valve prolapse was present, which had been noted since the initial heart failure diagnosis.

The patient underwent TV Duran ring annuloplasty and RA reduction on cardiopulmonary bypass (23 minutes) but without cardiac arrest. Intraoperative TEE after repair showed no TR with reported improvement in RV size and function. He was discharged on low-dose furosemide, which was stopped at 6 months of follow-up. By the second year of follow-up, however, moderate TR was again present along with moderate mitral regurgitation. In the years following valve repair, he suffered significant VT, requiring 2 endocardial ablations, antiarrhythmic therapy, and implantation of an ICD. He was diagnosed with ARVD/C 2 years after his TV surgery. His ECG is shown in Figure 1 (epsilon waves are noted). The patient died of accidental causes 5 years postoperatively.

Case 3
Tricuspid valve repair for moderate tricuspid regurgitation and isolated stage C, NYHA class II, isolated right ventricular heart failure

A 17-year-old girl presented after identification of an incidental holosystolic cardiac murmur on routine physical examination. Echocardiography at that time showed mild to moderate TR (normal RVSP 28 mm Hg) and RV dilation (RV internal diameter 3.9 cm). Over the following 2 years, she developed mild symptoms during significant exertion (NYHA class II), not requiring specific therapy. She also had an episode of VT (diagnosed as RV outflow tract VT) for which she had 1 endocardial ablation; no ICD was implanted. A cardiac magnetic resonance image showed moderate RV dilation (RV end-diastolic volume 131.25 ml/m²) with moderate global systolic hypokinesis (RV ejection fraction 30%), moderate TR (regurgitant fraction 40%), and normal LV function. As compared to previous studies, this study showed progression of TR, RV dilation, and deterioration in function; therefore surgical correction of TR was pursued for what was felt to be primary TR.

TV valvuloplasty was performed with closure of an accessory commissure of the anterior leaflet. Moderate TR persisted intraoperatively and therefore a modified De Vega annuloplasty (Reed) was performed. At this point, an intraoperative TEE still demonstrated moderate TR and chordal lengthening of the anterior TV leaflet was accomplished. The
| Sex/race            | Case 1 | Case 2 | Case 3                          |
|---------------------|--------|--------|---------------------------------|
| Age/presentation    | 50/syncope | 56/syncope | 17/incidental murmur |
| 2010 Task Force Criteria |        |        |                                |
| Structural alterations | Major  | Major  | Major                           |
| Tissue characterization | N/A    | N/A    | N/A                            |
| Repolarization abnormalities | Minor  | Major  | Major                           |
| Depolarization abnormalities | None   | Major  | Minor                           |
| Arrhythmias         | Major   | Minor  | None                            |
| Family history/genetics | None   | None   | Major/PKP2: heterozygous, c.224-3, C>G |
| Diagnosis           | Definite | Definite | Definite                        |
| Heart failure / procedure |        |        |                                |
| Age at procedure    | 66      | 69     | 19                              |
| Symptom class       | NYHA IV | NYHA II/III | NYHA II                         |
| Diuretics           | Yes     | Yes    | No                              |
| Procedure           | Bioprosthesis replacement after attempted repair | Ring annuloplasty | Suture annuloplasty and valvuloplasty |
| Echocardiographic features |        |        |                                |
| RV dilation         | Severe  | Moderate | Moderate–severe global HK       |
| RV function         | Severe global HK | Moderate–severe global HK | Severe global HK |
| TR                  | Severe  | Trace   | Severe                          |
| LV function         | Reduced, EF 30-40% | Reduced, EF 35-40% | Normal, EF = 60% |
|                      |         |         | Severe global HK                |
|                      |         |         | Moderate                         |
|                      |         |         | Normal, EF = 60%                 |
|                      |         |         | Severe global HK                |
|                      |         |         | Moderate                         |
|                      |         |         | Normal, EF = 79%                 |
|                      |         |         | Severe global HK                |
|                      |         |         | Moderate                         |
|                      |         |         | Normal, EF = 69%                 |

NYHA = New York Heart Association; RV = right ventricular; LV = left ventricular; TR = tricuspid regurgitation; HK = hypokinesis; EF = ejection fraction; NYHA = New York Heart Association; RV = right ventricular; LV = left ventricular; TR = tricuspid regurgitation; HK = hypokinesis; EF = ejection fraction.

*Most recent data or study available before surgery.

**Data or study at approximately 1 year postoperatively.
final intraoperative TEE showed mild residual TR with 2 distinct jets, yet TR was noted as moderate by the time of discharge. The procedure was conducted on cardiopulmonary bypass and the heart was arrested with aortic cross-clamping (times unknown).

The patient’s clinical symptoms (mild dyspnea on exertion and intermittent peripheral edema requiring as-needed diuretics) remained stable over the next 4 years, as did the severity of TR and RV dilation/dysfunction. By the fifth year of follow-up, there was progression of TR to severe and more RV dilation/dysfunction (RV internal diameter 3.9 cm and tricuspid annular plane systolic excursion 0.9 cm) with septal flattening consistent with RV volume overload (RVSP 30 mm Hg). This was associated with dyspnea occurring during moderate exertion with intermittent lower extremity edema requiring as-needed furosemide. A second endocardial ablation was also performed owing to recurrence of VT along with implantation of an ICD.

This patient was diagnosed with ARVD/C a year and a half after her initial TV operation. She was found to have 2 heterozygous mutations: (1) a splice site mutation involving a C > G base substitution at position c.224 of the plakophilin 2 gene (this mutation has previously been described in 1 patient with ARVD/C outside our registry); and (2) a missense mutation in the troponin T type 2 gene, which has been associated with hypertrophic and dilated cardiomyopathies.

Discussion

Main findings

We present 3 patients with significant TR and symptomatic RV dysfunction who underwent surgical intervention. Two patients (cases 1 and 2) showed symptomatic improvement following surgical correction of TR. Both of these patients were older men with prolonged, progressive heart failure courses and had developed severe TR with evidence of RV volume overload at the time of surgery, in the absence of significant pulmonary hypertension. In case 1, the patient underwent valve replacement after initial attempts at repair were inadequate. There was no significant TR at 18 months follow-up. In case 2, the patient underwent valve repair and initially showed significant radiologic and clinical improvement. Moderate TR was evident by 1 year of follow-up, although the patient remained clinically improved. The patient in case 3 underwent valve repair to correct what was considered primary TR. However, moderate TR was still present postoperatively, which progressed to severe TR by the end of follow-up. Only in case 1 had the patient been diagnosed with ARVD/C at the time of TV surgery.

Surgical correction of tricuspid regurgitation in arrhythmogenic right ventricular dysplasia/cardiomyopathy

In the general population, moderate to severe TR is associated with worse survival regardless of LVEF or pulmonary artery pressure. RV dysfunction secondary to TR is also an independent determinant of mortality. Although less well defined, both factors also seem to predict prognosis in ARVD/C. As the majority of functional TR is considered to be secondary to left-sided heart disease, surgical correction of functional TR is currently indicated only at the time of left-sided valve surgery. Isolated TV surgery, on the other hand, is indicated for patients with severe primary TR who either are symptomatic or have evidence of RV dysfunction. There is some evidence that early surgical intervention (RV end-systolic area <20 cm²) may improve outcomes and functional capacity in these patients. In patients with severe functional TR due to intrinsic RV changes, as is the case with ARVD/C, it is feasible that correction of TR could delay development of overt RV dysfunction, potentially due to reversal of chronic RV volume overload. However, one must also consider the potential worsening of RV function during cardiac surgery, secondary to septal damage or loss of pericardial integrity.

To the best of our knowledge, this is the first study to describe the course of multiple patients with definite ARVD/C who undergo surgical correction of TR. There are 5
isolated reports of surgical correction of TR in ARVD/C in the literature.\(^{10–14}\) Jiang et al.\(^{10}\) reported a case of a patient with long-standing heart failure who underwent TV repair in the setting of progressive and refractory symptoms. This patient experienced an early postoperative death due to low cardiac output. Similar to the patient in case 1, this patient had a depressed LVEF, although no preoperative hemodynamic data were available to help quantify the severity of LV failure or presence of pulmonary hypertension.\(^{10}\) Therefore, it is possible that this patient may have had significant pressure overload contribution to RV failure and TR, and thus, TV repair could have increased RV load and worsened RV failure. In the case described by Gwizdala et al.,\(^{11}\) a patient underwent TV repair for what was thought to be primary TR, similar to case 3. After an initial improvement during the first few years after surgery, the patient developed progressive biventricular heart failure and eventually was referred for cardiac transplantation.\(^{11}\) The third report describes a patient with severe TR and biventricular failure that underwent valve replacement along with epicardial defibrillator lead implantation.\(^{12}\) Improvement was noted in the immediate postoperative course; however, the patient was only followed to discharge.\(^{12}\) Finally, 2 authors report successful outcomes at long-term follow-up after TV repair. Both patients had severe TR, severe RV dilation, and biventricular heart failure, but also significant mitral regurgitation, and underwent simultaneous mitral valve procedures.\(^{13,14}\)

This issue of whether to repair or replace the tricuspid valve merits further discussion. In our series, the patient in case 1 underwent TV replacement (after attempted repair) and has had no TR identified during follow-up with significant improvement in symptoms. By contrast, the patients in cases 2 and 3, who both underwent repair procedures, saw return of TR during follow-up. In a recent study by Yiu et al.\(^{15}\) of patients undergoing TV repair, significant RV mid-cavity diameter dilation and TV tethering area were the 2 strongest predictors of postoperative adverse events. It was felt that inadequate surgical correction of TR and RV geometry were contributing factors to the adverse events. It is conceivable that patients with ARVD/C, who can have severe and progressive RV and TV structural changes, may fare better with replacement than repair. Additionally, many patients with ARVD/C will have ICD leads crossing the TV, which could theoretically damage the valve and contribute to worsening TR. In our series, only the patient in case 1 had an ICD before valve surgery was performed and this was left in place after valve replacement. Whether or not patients undergoing TV surgery should have lead revisions and/or epicardial lead placement at the time of surgery is unknown but may be worth considering.

**Conclusion**

In summary, our series suggests that surgical correction of functional TR in the context of significant RV dilation and RV volume overload could potentially improve heart failure symptoms in certain patients with ARVD/C. Further study of this treatment strategy, as well as defining the role of TV repair vs. replacement in this situation, is warranted.

**Acknowledgments**

The authors are grateful to the arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and families who have made this work possible.

**References**

1. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J 2010;31(7):806–814.
2. Te Riele AS, James CA, Philips B, et al. Mutation-positive arrhythmogenic right ventricular dysplasia/cardiomyopathy: the triangle of dysplasia displaced. J Cardiovasc Electrophysiol 2013;24(12):1311–1320.
3. Peramnanti B, Dragos AM, Pyraraia S-A, 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(9):1105–1113.
4. Saguner AM, Vecchietti A, Baldinger SH, et al. Different prognostic value of functional right ventricular parameters in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circ Cardiovasc Imaging 2014;7(2):230–239.
5. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol 2004;43(3):405–409.
6. Lee JW, Song JM, Park JP, Kang DH, Song JK. Long-term prognosis of isolated significant tricuspid regurgitation. Circ J 2010;74(2):375–380.
7. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(22):e188–e273.
8. Kim YJ, Kwon DA, Kim HK, Park JS, Han S, Kim KH, Kim KB, Sohn DW, Ahn H, Oh BH, Park YB. Determinants of surgical outcome in patients with isolated tricuspid regurgitation. Circulation 2009;120(17):1672–1678.
9. Buckberg GD, RESTORE Group. The ventricular septum: the lion of right ventricular function, and its impact on right ventricular restoration. European Journal of Cardio-Thoracic Surgery 2006;29(Supplement 1):S272–S278.
10. Jiang H, Zhang T, Shang L, Cui J, Liu J, Weng Y, Gu L, Li Y, Wu Q. A case of arrhythmogenic right ventricular cardiomyopathy/dysplasia in a middle-aged woman. J Cardiovasc Dis Res 2011;2(1):74–76.
11. Gwizdala A, Pospik H, Janus M, Gajek S, Straburzynska-Migaj E. From primary tricuspid regurgitation to arrhythmogenic right ventricular cardiomyopathy. Kardiol Pol 2013;71(10):1079–1081.
12. Yoda M, Tanabe H, Kishi M, Suma H. Alternative technique for implanting an epicardial cardioverter defibrillation patch during a tricuspid valve replacement. Interact Cardiovasc Thorac Surg 2011;12(4):628–630.
13. Maeda K, Sakagoshi N, Matsuura R, Shimazaki Y. Mitral valve repair, tricuspid valve annuloplasty, and ligation of coronary artery-pulmonary trunk fistula in a patient with arrhythmogenic right ventricular cardiomyopathy. J Card Surg 2011;26(3):274–276.
14. Sako H, Hadama T, Miyamoto S, Aina H, Wada T, Takahashi N, Yoshimatsu H. Successful surgical treatment of heart failure and ventricular tachycardia in a patient with arrhythmogenic right ventricular dysplasia with cardiomyopathy. Circ J 2005;69(8):996–999.
15. Yiu KH, Wong A, Pu L, et al. Prognostic value of preoperative right ventricular geometry and tricuspid valve tethering area in patients undergoing tricuspid annuloplasty. Circulation 2014;129(1):87–92.