Heart transplantation in arrhythmogenic right ventricular cardiomyopathy – experience from the Nordic ARVC Registry

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ABSTRACT

OBJECTIVE

There is a paucity of data on heart transplantation (HTx) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), and specific recommendations on indications for listing ARVC patients for HTx are lacking. In order to delineate features pertinent to HTx assessment, we explored the pre-HTx characteristics and clinical history in a cohort of ARVC patients who received heart transplants.

METHODS

Data from 31 ARVC/HTx patients enrolled in the Nordic ARVC Registry, transplanted between 1988 and 2014 at a median age of 46 years (14-65), were compared with data from 152 non-transplanted probands with Definite ARVC according to 2010 Task Force Criteria from the same registry.

RESULTS

The HTx patients were younger at presentation, median 31 vs. 38 years (p=0.001). There was no difference in arrhythmia-related events. The indication for HTx was heart failure in 28 patients (90%) and ventricular arrhythmias in 3 patients (10%). During median follow-up of 4.9 years (0.04-28), there was one early death and two late deaths. Survival was 91% at 5 years after HTx. Age at first symptoms under 35 years independently predicted HTx in our cohort (OR=7.59, 95%CI 2.69 – 21.39, p<0.001).

CONCLUSION

HTx in patients with ARVC is performed predominantly due to heart failure. This suggests that current 2016 International Society for Heart and Lung Transplantation heart transplant listing recommendations for other cardiomyopathies could be applicable in many cases when taking into account the hemodynamic consequences of right ventricular failure in conjunction with ventricular arrhythmia.

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) has been clinically recognised since the early 1980s, and as a unique form of cardiomyopathy since 1996.[1 2] ARVC involves wall thinning, cell necrosis and fibrofatty infiltration of the right ventricle, and frequently of the left ventricle as well. ARVC is characterized by ventricular tachyarrhythmia and risk of sudden death and, later, by heart failure.[1-4] ARVC is a hereditary disease with autosomal dominant inheritance with variable penetrance. A disease-causing genetic variant can be identified in 40-63% of probands, mainly in genes coding for cardiac desmosomal proteins.[3-5]

Earlier reports focused on ventricular tachycardia as the hallmark of the disease, with only a minority of cases progressing to overt heart failure.[1 6 7] Diagnostic Task Force Criteria were established in 1994 and revised in 2010.[8] Survival improved due to introduction of implantable cardioverter defibrillator therapy.[3 9] Thereupon, the number of survivors as well as the number of patients developing heart failure increased.[3-5] Consequently, some patients underwent heart transplantation (HTx) as highlighted in case reports[10-17] and a series of 18 patients from a large centre.[18]

In contrast to dilated or ischemic cardiomyopathy, which usually affects the left ventricle primarily, symptoms preceding HTx in ARVC are, in various degrees, caused by failure of the right ventricle, the left ventricle, or both, often complicated by arrhythmias.[10 17 18] In rare cases, indication for HTx is uncontrollable ventricular tachycardia – the so-called electric storm.[13 19] Since data on HTx in ARVC patients is sparse and ARVC is considered phenotypically difficult to characterize, the International Society for Heart and Lung Transplantation has refrained from providing specific recommendations regarding ARVC in its 2016 HTx listing criteria update.[20]

Contemporary data from dedicated ARVC registries with detailed disease-specific clinical information on disease diagnosis and progression are limited to a handful of case reports or a

small-cohort single-centre study.[18] By analyzing the Nordic ARVC Registry data[21 22] that covers major cardiogenetic clinics in Scandinavia, we sought to further explore the characteristics of ARVC patients undergoing HTx (including pre-HTx course and post-HTx survival) and to compare these patients with a background population of patients with ARVC not requiring HTx.

METHODS

The Nordic ARVC Registry (www.arvc.dk) was launched in June 2010 and has been recruiting patients with ARVC previously diagnosed using 1994 TFC and followed at one of eight tertiary care centres in Denmark, Norway or Sweden, covering a population of approximately 14 million. The registry also prospectively includes newly diagnosed patients with Definite ARVC according to 2010 Task Force Criteria, and these patients' first-degree relatives. Prospective follow-up information was available until April 2015 when data for the current analysis were retrieved. All patients who had undergone HTx were included and compared with a control group, which consisted of all 152 probands in the registry at the time of data retrieval with Definite ARVC according to 2010 criteria.[8]

We extracted pertinent clinical and interventional registry data as previously described.[21] HTx work-up data and indications were further evaluated by chart review. First ARVC-related symptoms, listed in Table, were defined as the 1st cardiac symptom warranting health-care contact. Left ventricular ejection fraction was obtained by echocardiography in all but 27 controls, in whom it was based on cardiac magnetic resonance. Symptoms of heart failure were categorized as New York Heart Association functional class II-IV heart failure symptoms. Right ventricular failure was defined as considerable impairment of right ventricular function by echocardiography, cardiac magnetic resonance or angiography. Left ventricular failure was defined as left ventricular ejection fraction ≤45%. Atrial fibrillation

was defined as at least one ECG-recorded event during follow-up. Electric storm was defined as ≥3 symptomatic ventricular tachycardia or implantable cardioverter defibrillator discharges within 24 hours. Regarding post-HTx outcome, only survival and mode of death were recorded. HTx indication (heart failure and/or uncontrollable ventricular tachycardia) was abstracted from patient charts.

Regional institutional ethics committees approved the study. In Denmark, registries do not require approval from an ethics committee, but approval was obtained from the Danish Data Protection Agency. The study complies with the Declaration of Helsinki.

Statistics

Data are presented as frequencies, or median and range, as appropriate. Comparison between groups was made using the Mann-Whitney U-test for continuous data, or using the 2-sided chi-square test for categorical data. Correlation was assessed using Spearman's rho. The association between unmodifiable risk factors presented at birth (gender, mutation carrying status and family history of ARVC) and the likelihood of HTx were analysed using the Kaplan-Meier curve analysis and Cox regression analysis with age at HTx as the time variable. Patients were censored at the date of the most recent clinical contact. Association between continuous variables and the likelihood of HTx was assessed using linear logistic regression analysis. A multivariate analysis using binary logistic regression with backward stepwise elimination and Wald statistics aimed at identification of clinical factors associated with HTx was also performed. Factors with a p-value of <0.10 in the univariable analysis were entered into the multivariable model. Statistical Package for Social Sciences version 20 was used for analysis.

RESULTS

31 ARVC patients were transplanted from 1988 onward, with 50% of the cases transplanted between 2010 and 2014. 23 of the patients fulfilled the 2010 Task Force Criteria, while eight earlier patients, transplanted 1988-2011, fulfilled the 1994 Task Force Criteria, thus adding up to 31/183 (17%) of all probands in the registry. In four patients, the ARVC diagnosis was established after HTx: of these patients, it was done by pathology findings in three patients, and by identification of an ARVC-causing mutation in one patient.

Table provides a summary of clinical and genetic characteristics of the study population. Clinical information from the pre-HTx work up in the HTx group is compared with data at most recent follow-up in controls. The HTx group developed ARVC symptoms at an earlier age than controls and, as expected, had more severe heart failure symptoms (New York Heart Association class III-IV) and a lower left ventricular ejection fraction. There was no significant difference between HTx patients and controls in gender or arrhythmic manifestations, including aborted cardiac arrest, electric storm, ventricular tachycardia ablation, implantable cardioverter defibrillator shock and atrial fibrillation, or the prevalence and scope of ARVC-related genetic variants.

Clinical factors associated with HTx

Neither gender (HR=1.08 95%CI 0.73 – 1.60, p=0.691), nor family history of ARVC (HR=1.51 95%CI 0.59 – 4.02, p=0.377), or desmosomal mutation carrying (HR=0.78 95%CI 0.38 – 1.64, p=0.518) was associated with the risk of HTx in the univariable Cox regression analysis.

Using linear logistic regression for continuous and binary logistic regression for dichotomized variables, including age at diagnosis and symptoms, gender, mutation-carrying status, history of AF and the history of ventricular arrhythmias, age at 1st symptom (β=-0.329, 95%CI -0.013 – -0.004, p<0.001), age at diagnosis (β=-0.207, 95%CI -0.009 – -0.001, p=0.006) and the history of atrial fibrillation (OR=2.61, 95%CI 0.91 – 7.47, p=0.074) were qualified for the

multivariable analysis. For the purpose of the multivariable analysis, age at 1st symptom and age at diagnosis were dichotomized by near median clinically relevant cut-off values. Age at first symptom < 35 years appeared to be the only independent predictor of HTx (OR=7.59, 95%CI 2.69 – 21.39, p<0.001).

ARVC course from initial manifestations to HTx

As presented in Table, the initial ARVC manifestation were arrhythmia-related symptoms (cardiac arrest, ventricular tachycardia, syncope, palpitations, dizziness) in >90% of both HTx and controls.

The time from the 1st ARVC symptom to HTx was variable (Figure 1, Table) and did not demonstrate any association with either gender (Rho = -0.01, p=0.97) or age at the 1st ARVC manifestation (Rho = -0.20, p=0.27).

An implantable cardioverter defibrillator was implanted in 25 patients (81%) at a median of 4.4 years (0.0-36) after the 1st ARVC symptom, and in three patients less than 6 months pre-HTx. The indication was secondary prophylaxis in 24 patients (96%) and primary prophylaxis in one patient (4%). 10 patients underwent catheter ablation for ventricular tachycardia; 3/10 had repeated procedures.

The clinical course of the disease was variable. Although arrhythmia-related symptoms remained dominating during the time up to HTx in 27 patients, in 10 there was a period ranging from 3-25 years without any reported ventricular tachycardia. Two patients progressed to end-stage heart failure within two years from the time of the 1st symptom, without accompanying ventricular tachycardia (one patient with atrial fibrillation). Two patients survived cardiac arrest, and four patients with an implantable cardioverter defibrillator suffered from electric storm. Atrial fibrillation at any time during pre-HTx period was observed in the minority of patients (n=6 or 19%), 5 of whom were older than 50 years at

the time of HTx. In two HTx patients, one of whom underwent HTx less than two years after 1st symptom, atrial fibrillation was the only reported arrhythmia.

HTx indications, pre HTx work-up and post HTx survival

HTx indication was mainly heart failure symptoms. This was the case for 28 patients (90%), of whom 18 had biventricular failure (58%), 9 had right ventricular (29%) and 1 left ventricular (3%) failure. Ventricular tachycardia was considered a contributing factor for HTx in 14 patients (50%) while in three patients it was the single indication for HTx (10%).

As demonstrated in Figure 2 and Table 1, 19 HTx patients (68% of 28 with available data) had echocardiographic evidence of left ventricular failure with reduced left ventricular ejection fraction ≤45%, in 9 patients it was ≤25%. In the control group, left ventricular failure was noted in only 17/134 (13%) ($p<0.001$).

Quantitative echocardiographic measurements performed within a year from ARVC diagnosis were available for 17 patients from HTx group and 112 control patients, while MRI was performed in a smaller subset (Table 2). Regardless of the imaging modality, patients who underwent HTx had significantly reduced right ventricular contractile function and larger right ventricular dimensions at the time of diagnosis.

By the time of HTx, the vast majority of patients from the HTx group had symptomatic heart failure corresponding to New York Heart Association class III or IV at pre-HTx work-up (94%), while only two non-transplanted ARVC patients reached this stage of heart failure by age 77 and 78, respectively (1.3%, $p=0.006$).

Before being accepted for HTx listing, all patients were on optimal therapy and without contraindications to HTx.[20] The use of antiarrhythmic drugs was documented in 19 patients including the use of amiodarone in 14, sotalol in 6 and flecainide in one. Vast majority of HTx patients received heart failure therapy including beta blocker in 15, angiotensin

converting enzyme inhibitors in 14, angiotensin receptor blocker (ARB) in three and diuretics in 15 patients. No patient was on mechanical circulatory assist device prior to HTx.

The median post-transplant follow-up time was 4.9 years (0.04-28, Table 1), with 6 patients being followed for over 10 years. One patient died two weeks post-HTx due to graft failure, and two patients died after 4.5 and 9.0 years, respectively, due to non-cardiac causes. Post-HTx survival was 91% at 5 years.

DISCUSSION

HTx in ARVC has recently come into focus, highlighted by a series of 18 patients including data on pre-HTx course from Johns Hopkins.[18] We report the largest ARVC-registry cohort of patients who have undergone HTx, including pre-HTx course and characteristics, HTx indications, and post-HTx follow-up. All patients were included in the Nordic ARVC Registry. These patients constitute 17% of all probands meeting 2010 Task Force Criteria for Definite ARVC in the registry, indicating that a considerable number of ARVC patients may eventually develop therapy-resistant symptoms warranting HTx. Even though the most recent report presenting US national long-term survival data is based on a larger number of 73 ARVC patients who underwent HTx in the USA by 2011,[23] the vast majority of transplanted patients had ARVC diagnosis established prior to implementation of the revised Task Force Criteria, while information on the pre-HTx disease course was lacking. The seemingly high rate of HTx in our registry, however, should not be interpreted as an accurate estimate of heart transplantation prevalence among patients with ARVC since patients might have been referred to the transplantation centres from hospitals not participating in the Nordic ARVC Registry thus leading to oversampling of HTx patients in the registry.

We compared data from the HTx group with a control group of ARVC probands who fulfilled the 2010 Task Force Criteria, including case history and functional data. We intentionally excluded family members in order to ensure that comparison of clinical characteristics is not biased by differences in application of diagnostic criteria unrelated to disease phenotype, since family members *a priori* have a less severe disease phenotype.

We found no significant difference in gender distribution or frequency of ARVC-causing genetic variants. The distribution of genetic findings was comparable to a recent large study by Groeneweg.[5]

The 1st ARVC symptom occurred at a younger age among HTx patients compared to controls and was an independent predictor of HTx, suggesting that early ARVC debut may be a risk factor as reported by Tedford.[18] Compared to controls, we found no differences in arrhythmia-related events (cardiac arrest, electric storm, ablation procedures or cardioverter defibrillator shocks), including atrial fibrillation. Therefore, we were unable to corroborate the findings of Saguner et al. regarding the association between atrial arrhythmias and adverse events in ARVC, including HTx.[12] Finally, left heart failure (ejection fraction≤45%) or severe symptoms of heart failure (functional class III-IV) were very common in the HTx group, but were rare among controls. More studies are needed to determine whether reaching New York Heart Association III heart failure severity status should be considered a trigger for HTx evaluation in patients with ARVC, as indicated by our findings.

Our data showed variable clinical history leading to HTx in patients with ARVC, which is in line with previous reports.[10 13 17 18] Case history may involve slow progression of symptoms over years or even decades,[18] as well as fast progression to HTx within two years of 1st symptom in patients with severe phenotype.[10 13 18] Although arrhythmic manifestations including ventricular arrhythmias and cardioverter defibrillator therapy were predominant

over the years, in this study as well as in another study,[18] some patients experienced several years of relative electrical stability before deteriorating.

A majority of HTx in ARVC is predominantly due to heart failure, in 90% of patients in this study and in 76% in another study.[18] In that study 62% of the patients transplanted for heart failure had biventricular involvement, data which is comparable to 18/28 (64%) in our cohort. It is, however, of note that left ventricular ejection fraction decrease in our study was somewhat modest (median 35%) compared to other cardiomyopathy patients undergoing HTx, which is usually <30%.[24] The fact that 50% of our patients with biventricular failure also had ventricular tachycardia may have rendered them hemodynamically vulnerable, aggravating their heart failure symptoms despite relatively well-preserved ejection fraction. In our study, 10% had ventricular tachycardia as the main HTx indication, compared to 24% in another report,[18] and compared to only 6% in the United States HTx registry.[23] Most patients undergoing HTx for arrhythmia nevertheless experience severe heart failure symptoms due to arrhythmia, and may also have biventricular involvement.[18]

We documented only three deaths post-HTx. The survival rate was 91% at 5 years and 81% at 10 years (with only six patients followed over 10 years). Our data compare favourably with current International Society for Heart and Lung Transplantation survival data after HTx due to cardiomyopathy (75% at 5 years and 60% at 10 years)[25] and is also somewhat better than recently reported US experience in HTx for ARVC (81% survival at 5 years).[23] To compare, recent Scandinavian post-HTx data for patients with non-ischemic cardiomyopathy (including ARVC) is approximately 80% survival at 5 years and 70% survival at 10 years.[26] The relatively good prognosis after HTx in ARVC patients may be partially attributable to comparatively low mean age at HTx, 46 years among our patients vs. 54 years in current International Society for Heart and Lung Transplantation data.[25] Further studies are needed in

order to document whether there are other contributing factors, such as a low pre-Htx pulmonary vascular resistance[17 19 23] or a comparatively low burden of other comorbidities.

Transplant indications

Htx listing indications in ARVC have not been widely addressed or discussed. The 2016 International Society for Heart and Lung Transplantation update on listing criteria state that, in general, indications for HTx in ARVC are similar to indications for other cardiomyopathies, but no references are noted. [20] The International Society for Heart and Lung Transplantation further acknowledges that no specific listing recommendations can be made since ARVC is a rare disease that is difficult to phenotypically characterize. In the 2015 International Task Force Consensus Statement on ARVC treatment, HTx is recommended for patients with either severe unresponsive heart failure or refractory ventricular arrhythmia. [4 18] Our data support the Task Force Consensus Statement. The finding that the vast majority of HTx in ARVC is due to heart failure also supports the 2016 International Society for Heart and Lung Transplantation HTx listing recommendation statement that, in general, indications for other cardiomyopathies can be used for ARVC. However, there are some specific features of ARVC hemodynamics with concurrent ventricular tachycardia that need to be taken into consideration.

In selected cases of ARVC with severe right ventricular failure evidence of Fontan-type circulation[27] in which pulmonary blood flow is passively propelled by the transpulmonary blood pressure gradient have been demonstrated.[17 19] Such patients are very sensitive to left ventricular dysfunction and ventricular tachycardia, both of which increase left ventricular filling pressure, thus diminishing transpulmonary driving pressure. For such patients, implantable cardioverter defibrillator therapy may be unreliable, since return to sinus rhythm

after defibrillator shock does not immediately restore pulmonary blood flow.[19] Fontan-type physiology may therefore constitute an auxiliary transplant indication in ARVC.[17 19]

We suggest that an ARVC patient who is in New York Heart Association functional class III-IV despite optimal treatment for heart failure and arrhythmia should be considered for HTx assessment, in agreement with 2016 International Society for Heart and Lung Transplantation listing recommendations regarding other cardiomyopathies.[20] Rare patients with poorly controlled ventricular tachycardia and Fontan-type circulation should be considered for listing at an early stage. The fact that these patients may not be eligible for bridging with a left ventricular assist device[16] due to right heart failure also favours early listing, as there is little advantage to postponing listing in view of the good results post-HTx results.[23]

Limitations of study

A few HTx patients were followed at another centre before HTx, limiting access to pre-HTx data. Some data for earlier patients were from a period when diagnostic modes were underdeveloped, some even from a period before ARVC was recognized. The lack of pre-HTx data on hemodynamics and maximal exercise capacity limits comparisons of our current ARVC HTx cohort with the general population of ARVC undergoing pre-HTx work up.

Conclusion

In a large cohort of ARVC probands, HTx was performed in 17%. Heart failure was the main indication for HTx in 90% of them, and ventricular tachycardia was the main indication for HTx in the other 10%. Young-age onset of ARVC and left ventricular involvement were associated with the need for HTx. Our data indicate that current 2016 ISHLT HTx listing recommendations developed for other cardiomyopathies appear to also apply in the context of

ARVC patients, taking into account hemodynamic consequences of right ventricular failure in conjunction with ventricular tachycardia characteristic of ARVC.

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CONFLICTS OF INTEREST

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FIGURE LEGENDS

Figure 1: Time from 1st ARVC symptom to HTx and post-HTx time in individual patients. † Deceased patients.

Figure 2: Left ventricular ejection fraction in 28/31 HTx patients (at pre-HTx work up) and 134/152 controls (at follow-up). Data obtained by echocardiography or cardiac magnetic resonance.

Table 1. Clinical history and data at pre-transplant work up (HTx) with corresponding data at follow-up in controls (C). Data expressed as frequencies (%) or median (range).

Data	**HTx**	**Controls**	**N (HTx/C)***	**P**
Patients	31	152		
Female	9 (29%)	51 (34%)		0.62
Genetic testing				
Patients tested	18 (58)	106 (70)		0.21
Pathogenic genetic variant, n (%)	11 (61)	69 (65)	18/106	0.74
Double genetic variants, n (%)	1 (9.1)	6 (8.7)	11/69	
Plakophilin 2 (PKP2)	8	46		
Desmoglein 2 (DSG2)	2	15		
Desmocollin 2 (DSC2)	1	3		
Transmembrane protein 43 (TMEM43)	1	2		
Ryanodine receptor 2 (RYR2)	0	1		
Clinical timeline (years)				
Age at 1st symptom	30.8 (7.2-51)	38.1 (5.8-76)	31/95	0.001
Time from 1st symptom to diagnosis	3.1 (0.0-36)	0.5 (0.0-23)	31/95	0.11
Age at diagnosis	41.1 (13-64)	42.2 (9.8-76)		0.06
Time diagnosis to HTx/follow-up (C)	8.2 (-1.5-31)†	6.5 (0.0-30)		0.56
Time 1st symptom to HTx/follow-up (C)	13.7 (1.4-38)	8.9 (0.5-35)	31/95	0.08
Age at Htx/follow-up (C)	45.9 (14-65)	51.5(20-82)		0.36
Post-HTx follow-up	4.9 (0.04-28)		31/-	
1st ARVC symptom			*27 †/152*	

Ventricular tachycardia	12 (39)	79 (52)		
Palpitations	3 (9.7)	25 (16)		
Dizziness	2 (6.5)	3 (2.0)		
Syncope	4 (13)	19 (12)		
Heart failure	2 (6.5)	0		
Cardiac arrest	3 (9.7)	14 (9.2)		
Chest pain	0	2 (1.3)		
Atrial fibrillation	1 (3.2)	0		
Unknown	4 (13)	10 (6.6)		
Evenst from 1st symptom to HTx/end of follow-up				
Cardiac arrest (without ICD)	2 (6.5)	6 (4.4)		0.34
Electrical storm	4 (13)	11 (7.2)		0.18
Atrial fibrillation	6 (19)	12 (7.9)		0.05
Ventricular tachycardia ablation	10 (32)	35 (23)		0.10
ICD implantation	25 (81)	117 (77)		0.91
ICD shock	13 (52)	56 (47)	25/117	0.73
NYHA III-IV	29 (94)	2 (1.3)		<0.001

* N=(31/ 152) unless otherwise stated. † In four patients, ARVC diagnosis was established post-HTx. ICD: Implantable cardioverter defibrillator. LVEF: Left ventricular ejection fraction. NYHA: New York Heart Association functional class.

Table 2. Quantitative assessment of right ventricular structure and function at diagnosis by echocardiography and cardiac magnetic resonance imaging (MRI). Numbers indicate availability of quantitative data.

	Imaging at diagnosis		P value
	HTx ARVC	**Control ARVC**	
Echocardiography	**N=17**	**N=112**	
PLAX RVOT, mm	56 (44-63)	38 (32-42)	<0.001
PSAX RVOT, mm	50 (43-56)	36 (32-41)	0.003
RVDD, mm	57 (49-65)	42 (36-48)	<0.001
RV FAC, %	20 (15-24)	35 (29-41)	<0.001
Cardiac MRI	**N=8**	**N=81**	
RVEF, %	28 (21-32)	40 (31-48)	<0.001
RVEDV, ml	264 (240-266)	209 (192-276)	0.252

PLAX – parasternal short axis view; PSAX – parasternal short axis view; RVOT – right ventricular outflow tract; RVDD – right ventricular diastolic diameter; RVEF – right ventricular ejection fraction; RVEDV – right ventricular end-diastolic volume; RV FAC - right ventricular fractional area change

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