Gender Difference in Idiopathic Right Ventricular Outflow Tract-Ventricular Tachycardia

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Background: Few studies have discussed gender differences in idiopathic right ventricular outflow tract-ventricular tachycardia (RVOT-VT). This study explored possible gender differences in electrophysiological characteristics and catheter ablation for idiopathic RVOT-VT in Taiwan.

Methods: Ninety-three patients (mean age 38.7 ± 15.5years, 30 males) were diagnosed as having idiopathic RVOT-VT between 1998 and 2010, and were enrolled and analyzed as part of our investigation.

Results: The age of onset, syncope episodes, underlying hypertension, diabetes mellitus, hyperlipidemia or family history of ventricular arrhythmias did not differ between males and females. Male patients had longer QRS width (99.9 ± 19.4 ms vs. 88.4 ± 20.7 ms, p = 0.02). Female patients had lower right ventricular mean voltage (3.0 ± 0.7 mV vs. 3.7 ± 0.9 mV, p = 0.03), and more low voltage zone over the right ventricular outflow tract free wall (27.0% vs. 6.7%, p = 0.02). Eighty-one patients received catheter ablation (23 males). The acute success rate, repeated catheter ablation rate and VT recurrence rate were similar between the genders.

Conclusions: Our study did reveal differences in electroanatomical characteristics by gender for patients who had idiopathic RVOT-VT, but overall outcomes after catheter ablation were similar.

Key Words: Gender • Right ventricular outflow tract-ventricular tachycardia

INTRODUCTION

Gender differences have been observed in the epidemiology, pathogenesis and clinical presentation of various ventricular arrhythmias.[1,2] For example, Brugada's syndrome is more common in men than in women, while idiopathic RVOT-VT, drug-related Torsade de Pointes and long QT syndrome are more common in women.[1,2] A higher mortality rate and sudden death rate have been documented in male patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) than in female patients with the same mutation.[3] Studies have identified triggers of RVOT-VT and found women tended to have frequent VT initiation during hormonal flux.[4] Few studies to date have addressed possible gender differences in electrophysiological characteristics of idiopathic RVOT-VT, other than epidemiological ones. The identifiable electroanatomical characteristics of each gender are also not understood. In Taiwan, idiopathic RVOT-VT is the most frequent type VT for electrophysiology study and ablation in the past decade. This study explored gender differences in electrophysiological characteristics and the results of catheter ablation for idiopathic RVOT-VT in Taiwan.

Received: January 19, 2013 Accepted: June 5, 2013

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METHODS

Study population

We enrolled a total of 93 patients (mean age 38.7 ± 15.5 years) who were diagnosed with idiopathic RVOT-

VT between 1998 and 2010. The diagnosis of VT was documented either by 12-lead resting electrocardiogram (ECG) or 24-hour holter ECG. Cardiac catheterization excluded the possibility of coronary artery disease. All patients received transthoracic echocardiography at the time of diagnosis and all other heart diseases, such as dilated cardiomyopathy, were excluded. We evaluated right ventricular (RV) function, regional RV wall motion, as well as left ventricular (LV) function, LV wall motion and LV ejection fraction (EF). RV dysfunction was defined as regional RV akinesia, RV dyskinesia, RV aneurysm, or RV EF less than 40%. ARVC/D was excluded by Task-Force criteria.[5]

Electrocardiographic analysis

Monomorphic VT was defined as VT with a uniform beat-to-beat surface QRS morphology. Electrocardiographic criteria were employed to identify VT origin, and all were RVOT-VT.[6] We analyzed right bundle branch block (RBBB) patterns, QRS width, repolarization abnormalities (T wave inversion in right precordial leads from V1 to 3), and prolonged corrected QT intervals (≥ 440 ms).

Electrophysiological study and electromechanical mapping

Standard electrophysiological study was performed on all patients after discontinuation of anti-arrhythmic agents for more than five half-lives. Programmed ventricular electrical stimulation[7] was performed with up to three extrastimuli delivered during sinus rhythm after eight paced ventricular cycle lengths. Induced VT with a duration longer than 30 seconds or concomitant hemodynamic compromise was classified as inducible sustained VT. The first test location was at the RV apex, while the next test site was the RVOT if sustained VT was not induced from the previous site. When electrical stimulation failed to induce sustained VT, we used intravenous infusion of isoprenaline (1-4 ug/min) with or without atropine. Sustained VT induced under the use of isoprenaline with or without atropine was defined as catecholamine-sensitive VT. We analyzed the location of the RVOT-VT origin using multiplane fluoroscopy, mainly the 60° left anterior oblique projection and the 30° right anterior oblique projection. If the VT origin was located to the anterior or posterolateral attachment of the RVOT, the patient was thought to have VT of a septal origin.[8]

We performed simultaneous electromechanical mapping during electrophysiologic study (EPS) using the NavX mapping system (NavX, St. Jude Medical, St. Paul, MN, USA). The mapping procedure included pace mapping during sinus rhythm, endocardial activation mapping, identification of diastolic potentials and entrainment mapping during VT. Entrainment was performed to identify the critical component of the VT circuit and for guidance of selective ablation. We used endocardial activation-sequence mapping to record the earliest endocardial activity and diastolic potentials during VT. Continuous recordings of RV endocardium voltage were done during sinus rhythm, and abnormal areas were defined as voltage setting of ≤ 1.5 mV on bipolar electrogram. Scar zones were defined as a voltage setting of < 0.5 mV, whereas areas with voltage between 0.5 mV and 1.5 mV belonged to low voltage zones. This facilitates the delineation of the culprit substrate for VT. We performed catheter ablation in those patients with inducible VT with standard radiofrequency energy delivered through 4-mm tipped deflectable ablation catheters. Twelve patients did not receive catheter ablation because relevant clinical VT was not induced during EPS. Acute success meant the absence of any inducible VT at the end of the catheter ablation procedure via electrical stimulation with or without isoprenaline. ECGs were checked soon after EPS or catheter ablation. After hospital discharge, the first outpatient follow-up time was arranged two weeks later and further follow-up visits were scheduled at three-month intervals. Surface ECGs and 24-hour holter ECG exams were arranged during serial outpatient follow-up. VT with RVOT origins documented on ECGs or 24-hour holter ECG exams was classified as VT recurrence.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and the comparisons between continuous data were performed using Student's t test. Comparisons of categorical data were performed using a Chi-square test with a Yates' correction or Fisher's exact test. Statistical significance was established at a p value of < 0.05. All statistical analyses were performed using commercial statistical SPSS version 17.0 software (SPSS, Chicago, IL, USA).

RESULTS

General characteristics

As shown in Table 1, there was no difference between genders in age of disease onset, diabetes mellitus, hyperlipidemia, previous syncope episodes or family history of ventricular arrhythmias.

Electrocardiographic differences

No differences existed between genders in respect to percentage of atrial arrhythmias and QTc prolongation. We found an RBBB pattern of QRS in four male patients (13.3%) and five female patients (7.9%), which was not statistically significant. The QRS width was longer in men as compared with women (99.9 ± 19.4 ms vs. 88.4 ± 20.7 ms, p = 0.02). The incidence of T-wave inversion in right precordial leads indicated no statistical differences between genders. Twenty male patients (66.7%) presented with clinically documented VT, while 50 female patients (79.4%) did. Most of them had monomorphic VT. Only two male patients and three female patients had multiple monomorphic VT or polymorphic VT (Table 2).

Ventricular substrate

There was no difference in LVEF between genders. Twenty-one percent of male patients had RV dysfunction compared to 19% of female patients (p = 0.85). The

Table 1. Baseline characteristics of male and female patients with idiopathic RVOT-VT

	Males (n = 30)	Females (n = 63)	p value
Age onset, years	44.8 ± 18.3	36.7 ± 14.1	0.09
BMI, kg/m^2	23.8 ± 2.7	24.0 ± 6.8	0.86
Syncope	43.3%	34.9%	0.43
Medical history			
Hypertension	20.0%	17.5%	0.77
Diabetes mellitus	10.0%	7.9%	0.51
Hyperlipidemia	20.0%	6.3%	0.06
Family history of ventricular arrhythmias	3.3%	3.2%	0.70

BMI, body mass index; RVOT-VT, right ventricular outflow tract-ventricular tachycardia.

Table 2. Electrocardiography and echocardiography characteristics in male and female patients with idiopathic RVOT-VT

	Males (n = 30)	Females (n = 63)	p value
Atrial arrhythmia (AF/AFL, AT)	30.3%	14.3%	0.07
QTc, ms	418.6 ± 34.4	432.3 ± 41.2	0.14
QTc prolonged (≥ 440 ms)	29.6%	34.5%	0.66
RBBB	13.3%	7.9%	0.32
QRS width, ms	99.9 ± 19.4	88.4 ± 20.7	0.02
Repolarization abnormalities*	10.0%	19.0%	0.21
Clinically documented VT	66.7%	79.4%	0.19
Multiple monomorphic VT or polymorphic VT	6.9%	5.0%	0.66
Transthoracic echocardiogram			
LVEF, %	57.8 ± 8.1	56. 9 ± 8.5	0.70
LV enlargement	3.4%	1.6%	0.53
LV hypokinesis	3.4%	6.3%	1.00
RV enlargement	6.9%	6.3%	1.00
RV regional dyskinesia	13.8%	20.6%	0.43

AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; EF, ejection fraction; LV, left ventricle; QTc, QT interval corrected for heart rate; RBBB, right bundle branch block; RV, right ventricle; RVOT-VT, right ventricular outflow tract-ventricular tachycardia; TWI, T wave inversion.

* T wave inversion in right precordial leads from V1 to 3.

percentage of RV dyskinesia was similar for male and female patients (13.8% vs. 20.6%, p = 0.43).

Electrophysiology study and electroanatomic mapping

Male patients had higher mean RV voltage than females did (3.7 ± 0.9 mV vs. 3.0 ± 0.7 mV, p = 0.03). Analyzing scar zones and low voltage zones at RVOT and RV, females had more low voltage zones at the RVOT free wall (27% vs. 6.7%, p = 0.02) as compared with males. The percentage of low voltage zones in other areas was similar between genders (male vs. female, RVOT septum, 10% vs. 12.7%, p = 0.50; RV body free wall, 16.7% vs. 30.2%, p = 0.17; RV body septum, 6.7% vs. 0%, p = 0.10). There was no statistical difference in the percentage of scar zone distribution between male and female (RVOT free wall, 6.7% vs. 15.9%, p = 0.18; RVOT septum, 3.3% vs. 7.9%, p = 0.37; RV body free wall, 13.3% vs. 23.8%, p = 0.24; RV body septum, 6.7% vs. 0, p = 0.10, Figure 1).

The outcome after catheter ablation

In total, 81 patients received catheter ablation (23 male patients), and the mean follow up time was 26.9 months (26.9 ± 32.8 months). The acute success rate was similar in the two groups (73.9% vs. 65.5%, p = 0.47). Despite that most patients had monomorphic VT, multifocal ablation sites were needed in 7 male patients and 13 female patients. We analyzed the successful ablation sites and the correlation with scar zone or low voltage zone and there were no differences between male and female patients. We performed successful ablation according to the result of pacemap locations in 34.8% of male patients and 36.2% of female patients. The overall VT recurrence rate was likewise similar between two groups (26.1% vs. 27.6%, p = 0.89). Three male and five female patients received catheter ablation a second time (Table 3).

DISCUSSION

Main findings

The present study focuses on gender differences in electroanatomic characteristics and catheter ablation in RVOT-VT, which, according to the author's best knowledge, have never been previously reported. Females had more low voltage zone in the RVOT free wall, lower mean RV voltage, and shorter QRS duration as compared with males. The acute success rate, repetitive ablation rate and VT recurrence rate did not differ between genders.

Gender differences in electrophysiological characteristics

Differences in electrophysiological characteristics between genders have been reported. Women have higher resting heart rates, longer QT intervals, shorter

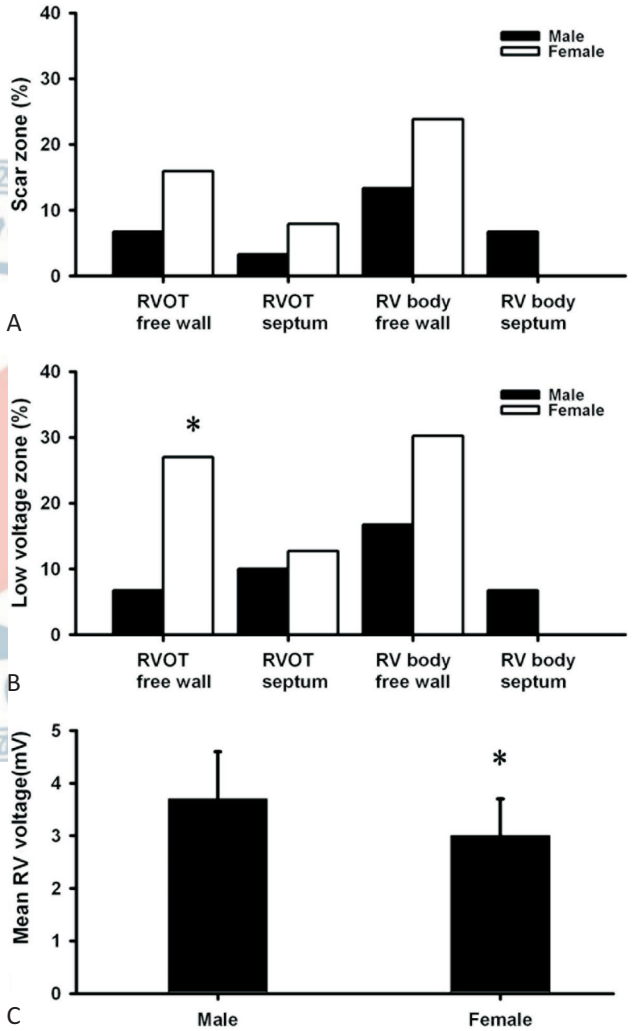

Figure 1. *Electroanatomic mapping showed that both genders had similar percentage of scar zone distribution (A). As for low voltage zones, females had more low voltage zones at the RVOT free wall as compared with males, while a similar percentage of low voltage zone was noted in other areas (B). Male patients had higher mean RV voltages than females did (C). * Indicates p < 0.05. RVOT, right ventricular outflow tract.*

Table 3. Ablation results for male and female patients with idiopathic RVOT-VT receiving catheter ablation

	Males (n = 23)	Females (n = 58)	p value
Baseline HR (beats/minutes)	71.1 ± 12.2	72.0 ± 15.1	0.79
Inducible sustained VT	24.1%	23.3%	0.93
Catecholamine sensitive	44.8%	55.0%	0.37
Multifocal ablation sites	41.2%	33.3%	0.57
Successful ablation site			
Scar zone	21.7%	17.2%	0.75
Low voltage zone	17.4%	19.0%	1.00
Pacemap location	34.8%	36.2%	0.90
Acute success	73.9%	65.5%	0.47
VT recurrence	26.1%	27.6%	0.89
Repeat ablation	13.0%	8.6%	0.41

HR, heart rate; RVOT-VT, right ventricular outflow tract-ventricular tachycardia.

sinus node recovery time, and longer ventricular effective refractory periods.[9] Various supraventricular arrhythmias also present gender differences. Gender differences in pulmonary vein and left atrium action potential characteristics were noted in the animal study.[10] In the human study, female gender with atrial fibrillation could predict the presence of superior vena cava ectopic beats.[12] Women have a higher prevalence of multiple accessory pathways and orthodromic atrioventricular reentrant tachycardia in those with preexcitation syndrome.[13] In view of atrioventricular nodal reentrant tachycardia, both the antegrade fast and slow pathways effective refractory periods in women were significantly shorter than those in men.[14] Nevertheless, limited information about ventricular arrhythmias was noted from currently available literature.

Women have longer ventricular effective refractory periods compared with men.[15] Women have higher incidence of congenital and acquired long QT syndrome, but less ventricular tachycardia/fibrillation-related sudden cardiac death.[9] In idiopathic ventricular tachycardia including RVOT-VT, gender-specific differences exist in the incidence and age distribution. The incidence of RVOT-VT in female is higher than that in males[9] but gender was not associated with the outcome after catheter ablation.[16] In the patients with idiopathic ventricular arrhythmias, males are prone to have tachycardia-induced cardiomyopathy.[9,16] The present study provides further evidence of gender differences in electroanatomic mapping. Females had shorter QRS duration, lower right ventricular voltage, and more low voltage zone in the RVOT free wall than males. Although the possible mechanisms are not clear, our findings suggest differences in ventricular remodeling between genders in patients with idiopathic RVOT-VT. The RVOT free wall was the prominent region, which was not associated with different VT incidences. Those findings suggest that ROVT low voltage might be the remodeling result after VT, rather than the cause. The outcome after catheter ablation was similar between genders, which was similar to the previous report.[16]

Mechanisms of gender differences

Several mechanisms have been proposed to explain the gender differences in arrhythmias, and one of those is associated with sex hormones.[17] Acute administration of 17 beta-estradiol can prolong ventricular repolarization, induce a higher incidence of early after-depolarization, and accentuate the proarrhythmic effects of cisapride.[17]

Sex hormones could regulate the expression of cardiac ion channels. Progesterone increases delayed rectifier K^+ current (I_{ks}) through the nitric oxide production pathway and prevents cyclic adenosine monophosphate enhancement of L-type Ca^{2+} current.[18]

Other possible mechanisms are different distributions of ion channels between genders. James et al.[19] reported gender-related differences in ventricular myocyte repolarization in the guinea pig. The I_{Ks}, and inward rectifier K^+ current were different between genders regardless of menstrual cycle. Gaborit et al.[20] further reported male and female human hearts have significant differences in ion-channel subunit composition, with female hearts showing decreased expression of a number

of repolarizing ion-channels.

The autonomic nerve system could also play the role. Autonomic regulation, contributing to different cardiac electrophysiology[21] might explain gender differences in various arrhythmias.[22-24] Arg16Gly in β2-adrenoceptor is significantly associated with idiopathic ventricular outflow tract tachycardias in the Chinese Han population,[25] which suggests the possible roles of sympathetic systems in RVOT-VT. In summary, gender differences might be attributed to multiple factors.

The outcome after catheter ablation

The gender differences in outcomes after catheter ablation for different arrhythmias have been reported. Outcomes of catheter ablation for atrial fibrillation in women were worse than in men, probably due to later referral and older age in the women in reported studies.[26] Similar ablation results were observed between the genders in atrioventricular nodal and atrioventricular reentrant tachycardia. With regard to idiopathic ventricular arrhythmias, no gender-related differences in outcome of catheter ablation have been reported.[16] This study also shows that successful ablation rates, recurrence rates, and repetitive operations were similar between genders. Idiopathic RVOT-VT is a relatively benign ventricular arrhythmia, and prognosis should rely on underlying conditions and comorbidities, rather than the arrhythmia alone. Ventura et al.[27] reported decennial follow-up in 133 patients (77 female; 39 + 13 years) with RVOT-VT for 135 + 68 months and 127 (95%) survived, while six (5%) died from noncardiac disease. In this study, ablation was performed in middle-aged groups with relatively few comorbidities and preserved left ventricular function. The modern technique of catheter ablation has a high success rate and low complications, which explains why the acute success rate and recurrence rate didn't differ between the two groups.

LIMITATION

In this study, some patients had RV regional dyskinesia on echocardiographic examination, while no cardiac magnetic resonance imaging (MRI) was performed to evaluate the presence of RV dysplasia. However, this is a universal limitation of registry data. According to previous report, MRI abnormalities could still be detected in patients with idiopathic RVOT-VT without other evidence of ARVC.[28]

CONCLUSIONS

Gender differences in electroanatomic characteristics were observed, but the outcome after catheter ablation was similar.

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