Gender and Age Differences in Candidates for Radiofrequency Catheter Ablation of Idiopathic Ventricular Arrhythmias

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**Background:** The prevalence, gender- and age-related differences, ablation success rate and inter-relationship between the origins of the idiopathic ventricular arrhythmias (I-VA) have not been clarified.

**Methods and Results:** A total of 625 consecutive patients with symptomatic, drug resistant I-VA (315 males and 310 females; mean age, 54±17 years; 218 ventricular tachycardias, 407 premature ventricular contractions) who underwent catheter ablation were studied. The patients were divided into 5 groups based on the VA origin: (1) outflow tract (OT)-VA, consisting of right ventricular (RV) OT-VA and left ventricular (LV) OT-VA; (2) inflow tract (IT)-VA, consisting of tricuspid annulus (TA)-free wall (FW)-VA, IT-septum-VA, and mitral (MA)-FW-VA; (3) LV-inferoseptum-VA; (4) LV-other-VA; and (5) RV-other-VA. RVOT-VA in women were 1.5 times more frequent than in men, while LVOT-VA were more frequent in men. The prevalence of LVOT origin I-VA increased with age compared to that for the RVOT. The mean age of MA-FW-VA patients (62±14 years) was higher than that of TA-FW-VA patients (51±18 years; P=0.03). The ablation success rate for RVOT-VA (88%) was higher than that for LVOT-VA (58%; P<0.0001). A multivariate analysis revealed that the patient age was one of the valuable predictors of a successful ablation (odds ratio=0.97; 95% confidence interval: 0.95–0.99; P=0.007).

**Conclusions:** Distinct gender and age differences were found in the incidence of I-VA according to the site of origin. (Circ J 2011; 75: 1585–1591)

**Key Words:** Age; Catheter ablation; Gender; Idiopathic; Ventricular arrhythmia

Diopathic ventricular tachycardia (VT) or premature ventricular contractions (PVC) most commonly arise from the right ventricular (RV) outflow tract (OT). However, previous reports have demonstrated other origins of VT/PVC, such as the left ventricular (LV) OT,6,7 LV epicardial sites8-11 around the mitral annulus (MA)8,12,13 and tricuspid annulus (TA).14 Furthermore, the VT originating from the LV infero-septum known as verapamil-sensitive VT are also classified into idiopathic VT.2,3,15 Although the characteristics of each VT/PVC were reported in those studies, no study has systematically clarified the prevalence, gender- and age-related differences, ablation success rate, and inter-relationship between the origins of the idiopathic ventricular arrhythmias (I-VA). Accordingly, the purpose of this study was to clarify these points.
inability of the patient to tolerate or unsuccessful treatment with at least 1 antiarrhythmic drug or patient refusal to take long-term antiarrhythmic medications (eg, young women who want to become pregnant). All patients had symptoms related to the I-VA almost every day.

Two-hundred eighteen patients had monomorphic VT, which was defined as 3 or more consecutive PVC, and the remaining 407 had PVC. The baseline characteristics of those patients, including the age, gender, and arrhythmia type (VT or PVC) were recorded. All patients had a normal 12-lead electrocardiogram (ECG) during sinus rhythm, and no structural abnormalities were apparent by physical examination or echocardiography. Before the ablation, 12-lead ECG were obtained at each clinic visit, and 24-h ambulatory Holter monitoring was carried out at least once. A conventional echocardiographic examination was also performed before the ablation procedure, and the LV end-diastolic diameter, LV ejection fraction, and LV mass was measured in all patients. Ethical approval was obtained from the hospital’s ethics committee, and all patients gave written informed consent before participation.

### Table 1. The Classification and Definitions of Idiopathic VA

<table>
<thead>
<tr>
<th>Classification of VA</th>
<th>Origin of VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) OT-VA</td>
<td>OT area</td>
</tr>
<tr>
<td>RVOT-VA</td>
<td>RVOT and pulmonary artery</td>
</tr>
<tr>
<td>LVOT-VA</td>
<td>Endocardium and epicardium* of the LVOT, and aortic sinus of Valsalva</td>
</tr>
<tr>
<td>(2) Inflow tract VA (IT-VA)</td>
<td>At or near the MA or TA</td>
</tr>
<tr>
<td>TA-FW-VA</td>
<td>TA FW</td>
</tr>
<tr>
<td>IT-septum-VA</td>
<td>TA septum and MA septum</td>
</tr>
<tr>
<td>MA-FW-VA</td>
<td>MA free wall</td>
</tr>
<tr>
<td>(3) LV-infero-septum-VA</td>
<td>LV infero-septum</td>
</tr>
<tr>
<td>(4) LV-other-VA</td>
<td>LV excluding sites (1), (2), and (3)</td>
</tr>
<tr>
<td>(5) RV-other-VA</td>
<td>RV excluding sites (1) and (2)</td>
</tr>
</tbody>
</table>

*Epicardium of the LVOT: Idiopathic VA in which the earliest ventricular activation was recorded in the distal area of the coronary sinus (the transitional area from the distal portion of the great cardiac vein to the proximal portion of the anterior interventricular vein) were classified as originating from the epicardium of the LVOT.**

VA, ventricular arrhythmias; OT, outflow tract; L(R)VOT, left (right) ventricular outflow tract; L(R)IV, left (right) ventricular; IT, inflow tract; M(T)A, mitral (tricuspid) annular; FW, free wall.

### Mapping and Catheter Ablation

After withdrawal of all anti-arrhythmic drugs, an electrophysiological evaluation and catheter ablation were performed as previously described. With fluoroscopic guidance, catheters were positioned high in the right atrium, at the RV apex, and in the RVOT and/or His bundle region. Programmed ventricular stimulation was performed from the RV apex and RVOT at 2 drive cycle lengths, with up to 3 extrastimuli. In addition, incremental burst pacing at a cycle length up to 250 ms was performed. If the clinical arrhythmia did not occur spontaneously and was not induced in the baseline state, intravenous isoproterenol (0.5–2.0 μg/min) was administered to induce the arrhythmia. During an episode of a clinical arrhythmia, activation mapping was performed. A 7-Fr quadripolar catheter with a 4-mm distal electrode, embedded thermistor, interelectrode spacing of 2.5-2.0 mm, and deflectable tip ( Biosense Webster, Diamond Bar, CA, USA and EP Technologies, San Jose, CA, USA) was used for mapping and ablation. Radiofrequency energy was applied at the site where the earliest ventricular activation was recorded. In 52 patients in whom a clinical arrhythmia could not be induced, catheter ablation was performed at the site where a perfect or near-perfect pace map was obtained. Radiofrequency energy was delivered using a maximum power of 35 to 50 W and a maximum electrode-tissue interface temperature of 55°C to 60°C.

### Definition of Successful Catheter Ablation and the Site of the Arrhythmia Origin

Successful catheter ablation met 3 criteria: (1) absence of spontaneous or induced clinical VA, both in the absence and presence of isoproterenol, at the end of the procedure; (2) absence of any clinical arrhythmias for over 48 h of ECG monitoring in the absence of anti-arrhythmic drugs; and (3) no recurrence of symptomatic arrhythmias in the absence of any anti-arrhythmic drug therapy during at least 3 months of follow-up.

The site of the VA origin was defined as the site where the earliest ventricular activation was recorded and/or a perfect pace map was obtained. The patients with VA were divided into the following 5 groups based on the VA origin (Table 1): (1) OT-VA, consisting of RVOT-VA and LVOT-VA; (2) inflow tract (IT)-VA, consisting of TA-free wall (FW)-VA, IT-septum-VA, and MA-FW-VA; (3) LV-infero-septum-VA

VT, ventricular tachycardia; VA, ventricular arrhythmia; PVC, premature ventricular contraction. Other abbreviations see in Table 1.

### Table 2. Prevalence, Age at Onset, Gender Characteristics, and Results of the Radiofrequency Catheter Ablation of Idiopathic VA

<table>
<thead>
<tr>
<th>Arrhythmia origin</th>
<th>No. (%)</th>
<th>VT</th>
<th>PVC</th>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Male/ Female</th>
<th>Success (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) OT-VA</td>
<td>490 (78)</td>
<td>156</td>
<td>334</td>
<td>52.8±16.6</td>
<td>227</td>
<td>263</td>
<td>0.86</td>
<td>382 (78)</td>
</tr>
<tr>
<td>RVOT-VA</td>
<td>331 (53)</td>
<td>105</td>
<td>226</td>
<td>50.7±16.1</td>
<td>135</td>
<td>196</td>
<td>0.68</td>
<td>290 (88)</td>
</tr>
<tr>
<td>LVOT-VA</td>
<td>159 (25)</td>
<td>51</td>
<td>108</td>
<td>57.1±16.8</td>
<td>92</td>
<td>67</td>
<td>1.37</td>
<td>92 (58)</td>
</tr>
<tr>
<td>(2) IT-VA</td>
<td>80 (13 )</td>
<td>27</td>
<td>53</td>
<td>61.6±15.8</td>
<td>46</td>
<td>34</td>
<td>1.35</td>
<td>58 (73)</td>
</tr>
<tr>
<td>TA-FW-VA</td>
<td>17 (3)</td>
<td>6</td>
<td>11</td>
<td>51.6±18.4</td>
<td>11</td>
<td>6</td>
<td>1.85</td>
<td>14 (82)</td>
</tr>
<tr>
<td>IT-septum-VA</td>
<td>34 (5)</td>
<td>9</td>
<td>25</td>
<td>65.9±13.5</td>
<td>16</td>
<td>18</td>
<td>0.89</td>
<td>17 (50)</td>
</tr>
<tr>
<td>MA-FW-VA</td>
<td>29 (5)</td>
<td>12</td>
<td>17</td>
<td>62.4±14.4</td>
<td>19</td>
<td>10</td>
<td>1.90</td>
<td>27 (93)</td>
</tr>
<tr>
<td>(3) LV-infero-septum-VA</td>
<td>27 (4)</td>
<td>2</td>
<td>27</td>
<td>39.3±18.7</td>
<td>22</td>
<td>5</td>
<td>4.4</td>
<td>27 (100)</td>
</tr>
<tr>
<td>(4) LV-other-VA</td>
<td>16 (3)</td>
<td>6</td>
<td>10</td>
<td>57.9±20.6</td>
<td>13</td>
<td>3</td>
<td>4.3</td>
<td>11 (69)</td>
</tr>
<tr>
<td>(5) RV-other-VA</td>
<td>12 (2)</td>
<td>2</td>
<td>10</td>
<td>60.1±9.4</td>
<td>7</td>
<td>5</td>
<td>1.4</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Total</td>
<td>625 (100)</td>
<td>218</td>
<td>407</td>
<td>53.6±17.1</td>
<td>315</td>
<td>310</td>
<td>1.01</td>
<td>486 (78)</td>
</tr>
</tbody>
</table>

VT, ventricular tachycardia; VA, ventricular arrhythmia; PVC, premature ventricular contraction. Other abbreviations see in Table 1.
Gender and Age in Idiopathic Arrhythmias

(also known as verapamil sensitive VA); (4) LV-other-VA; and (5) RV-other-VA. In this study, the I-VA in which the earliest ventricular activation was recorded around the transitional area from the distal portion of the great cardiac vein to the proximal portion of the anterior interventricular vein were classified as originating from the epicardium of the LVOT.

Statistical Analysis
Continuous variables are expressed as the mean±SD, and were compared using the Student’s t-test. Categorical variables were compared using a chi-square analysis using the Yate’s correction if necessary. A univariate and multivariate logistic regression analysis was used to identify the predictors of a successful catheter ablation. All parameters with a significance <0.10 in the univariate analysis were entered into the multivariate model. If a complete or quasi-complete separation was detected, the predictor variables showing separation were removed from the analysis. A P-value <0.05 was considered significant.

Results
Prevalence of I-VA
Among the 625 patients who received catheter ablation, 486 (78%) I-VA were ablated successfully, but the remaining 139 (22%) represented an ablation failure. The distribution of the arrhythmia origins is shown in Table 2. Approximately 78% of the 625 I-VA were OT-VA. Of those, 331 (53%) I-VA arose from the RVOT, and 159 (25%) from the LVOT. Eighty cases (13%) of I-VA were classi-
fied into IT-VA. LV-infero-septum-VA were found in 27 (4%) patients.

**Age Distribution**
The mean age of the patients with each type of I-VA is shown in Table 2. As shown in Figure 1, the prevalence of I-VA with an origin in the LVOT increased with age compared to that in the RVOT. The mean age of the patients with LVOT-VA was higher than that of RVOT-VA (P<0.0001). In the IT-VA, the mean age of the patients with MA-FW-VA was higher than that of TA-FW-VA (P=0.03). The number of those patients was small, however the tendency of the age distribution in the MA-FW-VA and TA-FW-VA was similar to that of the LVOT-VA and RVOT-VA, respectively.
Gender and Age in Idiopathic Arrhythmias

(Figure 2). The age distribution of the patients with PVC and VT arising from the OT and from the IT are shown in Figure 3. For both PVC and VT, there was a tendency that the right-sided VA (RVOT-VA and TA-FW-VA) occurred at a younger age than the left-sided VA (LVOT-VA and MA-FW-VA). The LV-infero-septum-VA were observed in younger patients.

Gender Differences

The gender differences in the incidence of various origins of I-VA are shown in Table 2. The LVOT-VA, TA-FW-VA, MA-FW-VA, LV-infero-septum-VA, LV-other-VA, and RV-other-VA were more common in males than females, whereas the incidence of RVOT-VA was 1.5 times more frequent in females than in males (male/female ratio; 0.68). The IT-septum-VA were distributed almost equally between males (16 patients) and females (18 patients). Although the number of patients with LV-infero-septum-VA and LV-other-VA was relatively small, those types of VA were observed 4 times more often in males than in females.

Figure 4 shows the age distribution for the OT-VA between males and females. There seemed to be no gender difference in the age distribution between the male and female LVOT-VA patients (Figure 4B). However, there were 2 peaks of the onset of RVOT-VA in both the male and female patients: the peaks were in the second and fifth decades of life in the female patients, and in the fifth and seventh decades in the male patients (Figure 4A). The RVOT-VA were more often observed in females in the second to third decade of life than in males.

The Ablation Success Rate

There was a difference in the ablation success rate between the VA origins (Table 2). The ablation success rate of RVOT-VA was significantly higher than that of LVOT-VA (P<0.0001). Among the LVOT-VA, the VA that originated from the epicardium of the LVOT were successfully eliminated in 1 of 11 patients (9.1%), and those arising from the aortic sinus of Valsalva in 73 (61%) of 119 patients. In the patients with IT-VA, the success rate of IT-septum-VA was lower than that of the other VA (17/34 [50%] vs. 41/46 [89%]; P=0.0003).

Predictors of Catheter Ablation

The LV-infero-septum VA origin variable was excluded from the analysis because the presence of this parameter perfectly predicted a successful ablation.19

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate OR (95%CI)</th>
<th>P value</th>
<th>Multivariate OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.96 (0.95–0.98)</td>
<td>&lt;0.0001</td>
<td>0.97 (0.95–0.99)</td>
<td>0.007</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.63 (0.43–0.93)</td>
<td>0.022</td>
<td>0.95 (0.54–1.65)</td>
<td>0.85</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.43 (0.28–0.65)</td>
<td>&lt;0.0001</td>
<td>0.79 (0.44–1.42)</td>
<td>0.43</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.51 (0.16–0.60)</td>
<td>0.0004</td>
<td>0.60 (0.29–1.30)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

The LV-infero-septum VA origin variable was excluded from the analysis because the presence of this parameter perfectly predicted a successful ablation.

OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

Discussion

Major Findings

The results of this study demonstrate the following findings: (1) there were gender differences in the incidence of I-VA according to their site of origin. In particular, patients with I-VA originating from the RVOT were more often observed in females than in males. The distribution of the gender differed for each origin of the I-VA. (2) The patients with I-VA arising from the LVOT and MA-FW were older than those
with origins from the RVOT and TA-FW, respectively. (3) There was a difference in the ablation success rate between the VA origins. (4) The age of the patients was one of the valuable predictors of a successful ablation.

Gender and Age Differences
Gender differences in the incidence have been reported for various types of arrhythmias. AV nodal tachyarhythmias and torsades de pointes in the setting of congenital or acquired long QT syndrome occur more frequently in females. In contrast, males show a higher incidence of atrial fibrillation and Brugada syndrome compared with females. Nakagawa et al analyzed data from patients with I-VA from their own series and from a review of peer-reviewed publications and concluded that I-VA arising from the RVOT in females were 2 times more frequent than in males. Because the analysis was based on the literature and not on epidemiologic data, the findings might not reflect the real incidence of the patients with I-VA. Although this study was a retrospective analysis, this was a large single-center comparison of I-VA. The origins of the I-VA were not determined by the ECG morphology but by the electrophysiological findings in our population. In our study, there was a female predominance of I-VA arising from the RVOT, whereas for the other VA origins, excluding IT-septum-VA, there was a distinct male predominance. The IT-septum-VA were distributed equally between males and females. Lerman et al reported that most forms of RVOT-VA are adenosine sensitive and are due to catecholamine-mediated delayed afterdepolarizations (DAD) and triggered activity. This form is mediated by the stimulation of cyclic adenosine monophosphate (cAMP), which results in an overload of intracellular calcium and an oscillatory release of calcium from the sarcoplasmic reticulum. A transient inward (I\textsubscript{Na}) current and corresponding DAD are generated from the Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger. Moreover, Yamawake et al investigated the vagal stimulation and pharmacological responses of I-VA arising from the LVOT and suggested that the mechanism of the LVOT-VA was mostly due to cAMP-mediated triggered activity, similar to that of RVOT-VA. However, the mechanism of left-sided I-VA might be not only DAD but also re-entry. This is because sometimes discrete sharp potentials were recorded at the ablation site of the left-sided VA.

The pathological mechanisms for gender related differences in I-VA remains unknown. Experimental data on gender differences of the electrophysiological properties of cardiac repolarization showed gender-related variations in the cardiac K\textsuperscript{+} channel caused by gonadal steroid effects. Marchlinski et al reported that the hormonal fluxes during premenstrual, gestational, and perimenopausal periods could be triggers for RVOT-VT initiation. These findings suggested that sex hormonal effects were one of the possible mechanisms for gender differences in patients with I-VA arising from the RVOT. The 2 peaks in the onset of the RVOT-VA found in the female patients in this study might be partially due to sex hormonal effects. However, LVOT-VA had a male predominance in our population. The patients with LVOT-VA were older than those with RVOT-VA. It is suggested that the patients with LVOT-VA are less affected by gonadal hormones than those with RVOT-VA. Another important consideration is that the mechanism of LVOT- or LV-VA may be re-entry in some cases. Some previous reports have shown that females have a longer QT interval and repolarization due to the androgen effects. However, Nakagawa et al reported that the transmural dispersion was smaller in females than in males because the interval between the apex and end of the T wave was relatively shorter in females. The smaller transmural dispersion might protect females from re-entrance arrhythmias.

In our population, the prevalence of I-VA with an origin in the LVOT increased with age as compared to that in the RVOT. The tendency of an age distribution was also observed in the patients with IT-VA. However, the mechanism of this age distribution remains unknown. A recent study using a heart rate variability analysis demonstrated that sympathetic tone increased with age. It was suggested that the increasing sympathetic tone with age might cause a shift in the I-VA origin from the right side of the heart to the left side. However, no supporting data for this hypothesis were provided in this study.

The Predictor of a Successful RFCA
In the present study, there was a distinct age difference in the origins of the I-VA, and the age of the patient was an independent predictor of a successful ablation. The successful ablation rate of the IT-septum-VA was low because the arrhythmia origin was close to the AV node and His bundle and because there was a high risk impairing those. The successful ablation rate of I-VA arising from anatomically complicated properties, namely the LVOT-VA arising from the epicardium and aortic sinus of Valsalva, was also relatively low. All of those I-VA were often found in older people, but both the RVOT-VA and MA-FW-VA had a high successful ablation rate and were found in young people. Those distinct differences in the age and success rate of the catheter ablation among the VA origins might partially explain why the age of the patient was one of the valuable predictors of a successful ablation.

Study Limitations
First, in this study, all patients underwent RF catheter ablation and were symptomatic I-VA patients who were resistant to drugs or who refused to take long-term anti-arrhythmic medications. Most patients were adult patients who came and consulted the doctors at the Cardiovascular Division. However, the total number of patients that were children or adolescents was small, and no babies or infants were included. Therefore, the information on those younger I-VA patients was insufficient, and our results do not represent the general and overall prevalence and characteristics of I-VA. Second, intensive interviews about hormonal fluxes, such as the onset of menses, age of menopause, and effect of the menstrual cycle on the symptoms and occurrence of I-VA were not performed in the female patients in this study. Therefore, the detailed information on the relationship between I-VA and female hormones was not clarified. Third, the detailed nature of the PVC, such as the total number of PVC couplets and the coupling interval, was not assessed. A further prospective study with a larger sample size, investigated at multiple centers and including patients with a younger age and those treated by medication only, might be needed to clarify the points described above.

Conclusions
Distinct gender and age differences were found in the incidence of idiopathic VA according to their site of origin. There was a difference in the ablation success rate between the VA origins.
Disclosure

No author has a relationship with the industry.

References