Effect of oestrogen replacement therapy on idiopathic outflow tract ventricular arrhythmias in postmenopausal women

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Summary
Background. — Sex hormones and gender differences are associated with the occurrence of ventricular arrhythmias.
Aim. — To investigate the relationship between sex hormones and idiopathic outflow tract ventricular arrhythmias (IOTVA), and the effect of oestrogen replacement therapy on IOTVA, in postmenopausal female patients.
Methods. — Plasma sex hormone concentrations and ventricular arrhythmia counts were estimated in postmenopausal patients with IOTVA and control postmenopausal women. The effect of oestrogen replacement therapy on IOTVA was observed in postmenopausal patients with IOTVA.
Results. — The concentration of oestradiol in postmenopausal patients with IOTVA was significantly lower than that in control postmenopausal women (8.4 ± 3.4 vs 36.9 ± 12.8 pg/mL, respectively; P < 0.001). The ventricular arrhythmia count in postmenopausal patients with IOTVA was significantly higher than that in controls (10,171 ± 6091 vs 209 ± 468 counts/24 hours, respectively; P < 0.001). After 3 months of oestrogen replacement therapy, the ventricular arrhythmia count was significantly lower than that before therapy (3958 ± 1972 vs 10171 ± 6091 counts/24 hours, respectively; P < 0.001).

Abbreviations: IOTVA, idiopathic outflow tract ventricular arrhythmias; LVOT, left ventricular outflow tract; PVC, premature ventricular contraction; RVOT, right ventricular outflow tract.
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Oestrogen and arrhythmias

Conclusion. — This study showed that the concentration of oestradiol was lower in postmenopausal patients with IOTV A than in control postmenopausal women, and that oestrogen replacement therapy can inhibit effectively the genesis of IOTVA.

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Résumé

Justification. — Les hormones sexuelles et le sexe sont associés à la survenue d’arythmies ventriculaires.

Objectif. — Évaluer les relations entre le taux d’hormones sexuelles et la survenue d’arythmies ventriculaires idiopathiques naissant de la chambre de chasse ventriculaire gauche (IOTVA), ainsi que les excès d’un traitement estrogénique substitutif sur la survenue de ces arythmies ventriculaires chez des femmes ménopausées.

Méthode. — Les concentrations plasmatiques d’hormones sexuelles, et le comptage des arythmies ventriculaires ont été estimés chez des femmes ménopausées ayant des arythmies ventriculaires idiopathiques (IOTVA), et comparés à des femmes ménopausées témoins. L’effet du traitement estrogénique substitutif sur les IOTVA a été observé chez des femmes ménopausées, et présentant de telles arythmies ventriculaires.

Résultat. — Le taux d’œstradiol chez des femmes ménopausées ayant des IOTVA est significativement moindre comparativement aux femmes ménopausées témoins (8,4 ± 3,4 vs 36,9 ± 12,8 pg/mL, respectivement ; p < 0,001). Le taux d’arythmie ventriculaire chez les femmes ménopausées avec IOTVA était significativement plus élevé que chez les témoins (10,171 ± 6091 vs 209 ± 468 coups/24 heures, respectivement ; p < 0,001). Après trois mois de traitement estrogénique substitutif, le taux d’arythmie ventriculaire était significativement moindre qu’avant traitement (3958 ± 1972 vs 10,171 ± 6091 coups/24 heures, respectivement ; p < 0,001).

Conclusion. — Cette étude montre que le taux d’œstradiol est moindre chez les femmes ménopausées ayant des arythmies ventriculaires idiopathiques (IOTVA) comparativement à des femmes ménopausées témoins et qu’un traitement estrogénique substitutif peut inhiber efficacement la génèse de ces arythmies ventriculaires.

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Background

Ventricular tachycardia or frequent PVCs arising from the left and right ventricular outflow tracts in patients without apparent structural heart disease are called idiopathic outflow tract ventricular arrhythmias. Women have a higher prevalence of idiopathic right outflow tract ventricular arrhythmias, while men have a higher prevalence of idiopathic left outflow tract ventricular arrhythmias [1,2].

Sex hormones and gender differences have been reported be associated with the occurrence of ventricular arrhythmias [3–6]. Our previous study showed that the concentration of oestradiol in male patients with IOTVA was significantly decreased. In addition, we found that the ventricular arrhythmia count was significantly negatively correlated with the concentration of oestradiol in male patients with IOTVA [7]. However, the changes in sex hormone concentrations in postmenopausal female patients with IOTVA, and the effect of oestrogen replacement therapy on IOTVA, remain unknown. In the present study, we investigated the relationship between sex hormones and IOTVA, and the effect of oestrogen replacement therapy on IOTVA, in postmenopausal women.

Patients and methods

Study population and data collection

This clinical protocol was approved by the institutional medical ethics committee and was conducted according to the ethical guidelines outlined in the Declaration of Helsinki. We evaluated 35 consecutive postmenopausal female patients with IOTVA who agreed to participate in the study. The participants received oestrogen replacement therapy (conjugated equine oestrogen, 0.625 mg/day for 3 months) from Renmin Hospital of Wuhan University. Thirty-five age-matched postmenopausal women without IOTVA who also agreed to participate in the study were used as a control group; these women were selected randomly from the municipal population registry in Wuhan City. Both groups underwent the following tests: physical examination; chest X-ray; laboratory values; echocardiography with wall motion analysis; electrophysiological study and/or 12-lead electrocardiographic monitoring to exclude others types of arrhythmia; and Doppler screening to exclude the presence of structural heart disease. Potential participants were excluded if they were aged > 70 years, had a disease other than IOTVA (including fever, coronary artery disease, others types of arrhythmia, hypertension, endocrine secretion,
Table 1 Characteristics of postmenopausal women with and without idiopathic outflow tract ventricular arrhythmias.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n = 35)</th>
<th>IOTVA (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 ± 5</td>
<td>54 ± 5</td>
</tr>
<tr>
<td>Smokers (% of patients)</td>
<td>0.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Alcohol drinkers (% of patients)</td>
<td>5.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.2 ± 3.2</td>
<td>22.8 ± 3.6</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>61 ± 3</td>
<td>62 ± 3</td>
</tr>
<tr>
<td>PVC count (number of counts/24 hours)</td>
<td>209 ± 468</td>
<td>1,017 ± 6091*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73.7 ± 8.6</td>
<td>74.6 ± 9.3</td>
</tr>
<tr>
<td>Luteinizing hormone (range) (mLU/mL)</td>
<td>27.8 ± 8.9 (9.4—40.1)</td>
<td>24.3 ± 9.6 (11.2—39.2)</td>
</tr>
<tr>
<td>Progestogen (range) (ng/mL)</td>
<td>0.49 ± 0.19 (0.10—0.67)</td>
<td>0.51 ± 0.20 (0.12—0.70)</td>
</tr>
<tr>
<td>Oestradiol (range) (pg/mL)</td>
<td>36.9 ± 13.8 (16.7—67.1)</td>
<td>8.4 ± 3.4* (4.6—12.8)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.92 ± 0.17</td>
<td>3.88 ± 0.20</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>142.2 ± 1.7</td>
<td>143.1 ± 1.8</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.38 ± 0.18</td>
<td>2.33 ± 0.19</td>
</tr>
</tbody>
</table>

IOTVA: idiopathic outflow tract ventricular arrhythmias; PVC: premature ventricular contraction. Data are mean ± standard deviation unless otherwise indicated. The reference values for luteinizing hormone, progestogen and oestradiol concentrations in healthy postmenopausal women were 5.0 to 52.3 mLU/mL, 0.06 to 0.73 ng/mL and 13.0 to 93.3 pg/mL, respectively.

* P < 0.05, compared with controls.

metabolic diseases, etc.) or if they had taken any medication within the previous 2 months.

Blood samples for analysis of basal hormone concentrations were obtained between 8:00 am and 9:00 am after an overnight fast. Concentrations of plasma sex hormones (including luteinizing hormone, oestradiol and progestogen) were measured using commercially prepared immunoassay kits according to the manufacturer’s instructions (ADVIA Centaur Immunoassay Assay System, Bayer, Germany). Serum potassium, sodium and calcium concentrations were measured with standard laboratory techniques on a Hitachi 912 Analyzer (Roche Diagnostics, Basel, Switzerland). PVCs were defined as identifiable premature QRS complexes (premature with respect to the P wave). Other multipart forms of PVCs, such as bigeminy (two consecutive PVCs), salvo (three consecutive PVCs) and ventricular tachycardia (four or more consecutive PVCs), were all included in the PVC count. The average PVC count (number of counts/24 hours) was assessed by 72-h, 12-lead electrocardiographic monitoring (GE Healthcare, Milwaukee, WI, USA). The 12-lead electrocardiogram (ECG) diagnostic criteria for idiopathic right outflow tract ventricular arrhythmias are a wide QRS complex tachycardia with a left bundle branch block pattern and an inferior axis [8]. The 12-lead ECG diagnostic criteria for idiopathic left outflow tract ventricular arrhythmias are an S wave in lead I and an R-wave transition in leads V1 or V2; the absence of an S wave in leads V5 or V6 suggests a supravalvular location, whereas an S wave in leads V5 and V6 indicates an infravalvular location [9].

Statistical analysis

All values were expressed as means ± standard deviations or the percentage of incidence. The chi² test or Fisher’s exact test was used to compare proportions. Student’s t test was used for comparisons between groups. The paired t test was used for comparisons before and after oestrogen replacement therapy. Statistical significance was assumed if P was less than 0.05.

Results

Clinical characteristics

As shown in Table 1, there were no differences between postmenopausal patients with IOTVA and control postmenopausal women in terms of mean age (P = 0.99), mean body mass index (P = 0.86), mean ejection fraction (P = 1.00), proportion of smokers (P = 1.00) and proportion of alcohol drinkers (P = 1.00). In the IOTVA group, 68.6% (24/35) patients had IOTVA arising from the RVOT. There were no differences in serum concentrations of potassium, sodium or calcium between the two groups (P = 0.95, 1.00 and 1.00, respectively). There were no differences in the concentrations of luteinizing hormone (P = 0.28) and progestogen (P = 0.58) between the two groups. However, the concentration of oestradiol in postmenopausal patients with IOTVA was significantly lower than that in control postmenopausal women (P < 0.001). Most ventricular arrhythmias were shown
as PVCs; the ventricular arrhythmia count in postmenopausal patients with IOTVA was significantly higher than that in control postmenopausal women ($P < 0.001$).

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After 3 months of oestrogen replacement therapy, postmenopausal patients with IOTVA had no change in heart rate compared with before therapy ($73.9 \pm 8.9$ vs $74.6 \pm 9.3$ beats/min, respectively; $P = 0.83$). However, the ventricular arrhythmia count was significantly decreased compared with before therapy ($3958 \pm 1972$ vs $10,171 \pm 6091$ counts/24 hours; $P < 0.001$).

**Discussion**

The most common forms of idiopathic ventricular arrhythmias arise from the RVOT; idiopathic ventricular arrhythmias arising from the LVOT, although less common, are also observed [1,2]. IOTVA has been demonstrated to have a unique arrhythmogenic substrate and electropharmacological profile, including RVOT and LVOT arrhythmias; in general, these are adrenergically mediated and sensitive to lower intracellular calcium (e.g. adenosine and verapamil). Despite disparate sites of origin, previous studies suggest a common arrhythmogenic mechanism between RVOT and LVOT arrhythmias, and suggest that arrhythmias from both of these sites appear to be caused by triggered activity due to cyclic adenosine monophosphate-mediated, calcium-dependent, delayed afterdepolarizations [1,2,10,11].

A growing body of evidence has demonstrated that changes in sex hormone concentrations and gender differences may affect ventricular repolarization and may be associated with the occurrence of ventricular arrhythmias [3–6]. Philp et al. [12] showed that 17β-oestradiol could exert an antiarrhythmic effect via calcium channel inhibition during myocardial ischemia. Ullrich et al. [13] further demonstrated that 17β-oestradiol has a calcium channel inhibitory effect. These results indicated that a reduction in the 17β-oestradiol concentration may exert a proarrhythmic effect and could lead to calcium channel activation.

In the present study, we found that the concentration of oestradiol, but not of luteinizing hormone and progesterone, was significantly decreased in postmenopausal patients with IOTVA, which may lead to calcium channel activation and exertion of a proarrhythmic effect; this is consistent with the mechanism of IOTVA [1,2,10,11]. In addition, we found that oestrogen replacement therapy could inhibit significantly the arrhythmia count in postmenopausal patients with IOTVA. This result further suggested that the genesis of ventricular arrhythmia was associated with a reduction in oestradiol concentration in postmenopausal patients with IOTVA. However, Gokce et al. [14] showed that oestrogen replacement therapy could increase the frequency of arrhythmia (no statistical significance) in healthy postmenopausal women, which may be attributable to different study conditions (one study was conducted under physiological conditions whereas the other was conducted under pathological conditions); this needs future study. Recently, Chen et al. [15] demonstrated that 17β-oestradiol reduced vulnerability to ventricular arrhythmia in infarcted rats, indicating that oestrogen may exert an antiarrhythmic effect under pathological conditions. These results suggest that “lower oestradiol concentration” may be an important “substrate” for the genesis of IOTVA and that oestrogen replacement therapy may have an antiarrhythmic effect.

In conclusion, this study showed that the concentration of oestradiol was reduced in postmenopausal female patients with IOTVA compared with in control postmenopausal women, and that oestrogen replacement therapy inhibited effectively the genesis of IOTVA.

**Study limitation**

Overall, our study included only a small number of Chinese patients; a future study with a large cohort will be needed. The precise mechanism underlying our observation and its clinical relevance require future elucidation.

**Conflict of interest statement**

None.

**Acknowledgement**

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