SUCCESSFUL CONTROL OF REFRACTORY VENTRICULAR PREMATURE BEAT WITH AN ESTROGEN-PROGESTERONE COMPOUND

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Drug resistant ventricular premature contractions (VPCs) in a 35-yr-old woman were successfully controlled with a contraceptive agent containing estrogen-progesterone. The VPCs in this patient always showed an R on T phenomenon resulting in occasional short run of ventricular tachycardia. Apart from the VPCs, her ECG exhibited no abnormalities.

The family history revealed 9 instances of sudden unexpected death over 3 generations. The findings of myocardial biopsy of the right ventricular endocardium were characteristic of cardiomyopathy. This report discusses the possibility that a contraceptive agent successfully suppressed VPCs in a particular woman who showed a close relation between a certain period of her menstrual cycle and the occurrence of VPCs.

A number of familial occurrences of sudden death have been reported.1–3 It appears that many of these may be precipitated by ectopic tachyarrhythmia. It is generally recognized that ventricular premature contractions (VPCs) in patients with cardiomyopathy tend to be resistant to conventional drug therapy. The present report describes the successful control of refractory VPCs with a contraceptive agent in a 35-yr-old woman with cardiomyopathy whose family included 9 cases of sudden unexpected death over 3 generations.

Case report
A 35-yr-old woman was admitted to the University Hospital, Kyorin University, for evaluation of cardiac arrhythmia. At the age of 15 yr, she had suddenly become pale and noticed vertigo, while playing soft-ball in a yard. At this time, cardiac examinations and an electrocardiogram were said to be normal. She remained well without cardiac symptoms until the age of 25 yr, when she experienced her first syncopal attack. At this time, she fainted suddenly without any prodromal symptoms while cooking in a kitchen. The attack lasted about for 5 min. Following this first syncopal attack, she occasionally noticed palpitations and dizziness, which appeared to be independent of exercise or emotional excitement. Over the past 10 yr, she has experienced 3 further syncopal attacks, at the ages of 28, 34, and 35 yr. Immediately after each attack, she was taken to a near-by hospital, where physical examinations, electrocardiograms and electroencephalograms failed to reveal any abnormal findings, which could be responsible for the syncopal attacks. On the occasion of the last attack, she became conscious when she found her 3-yr-old son jumping on her back. The jumping action may have played a role of extracardiac

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massage. Over the following 6 months, dizziness and palpitations increased in frequency and severity. On the day after the last syncopal attack, she was referred to our hospital for cardiac evaluation and treatment. On examination, the patient was found to be a well-developed woman who was comfortable at rest. Her blood pressure was 124/80 mmHg. The apical pulse rate was 80/min and irregular. There was no cervical venous distension, hepatomegaly or pretibial edema. Her family history revealed 9 instances of sudden unexpected death over 3 generations. The affected members and ages of death are shown in Fig. 1. The average age at sudden death was 32 yr. Death was heralded by syncopal episodes in all victims but no other signs or symptoms of cardiovascular disease were noted. The ECG on admission revealed frequent VPCs, all of which fell upon the preceding T wave ("R on T" phenomenon). The Q-Tc interval was normal. Immediately after admission, ECG monitoring was initiated. During such observation, it was frequently found that repetitive runs of ventricular tachycardia (VT) were initiated by VPC showing the "R on T" phenomenon (Fig. 2). During attacks of VT she complained of severe palpitations but never fell into syncope. These attacks disappeared spontaneously or on knocking of the precordium with her
Fig. 3. Myocardial biopsy of the right ventricular endocardium. The myocardial tissues are surrounded by connective tissue and exhibit brown degeneration.

**AGENTS**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Max. Dose</th>
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<tbody>
<tr>
<td>Lidocaine</td>
<td>60 mg</td>
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<tr>
<td>Disopyramide</td>
<td>400 mg</td>
</tr>
<tr>
<td>Propranolol</td>
<td>400 mg</td>
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<tr>
<td>Ajmaline</td>
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<tr>
<td>Pindrol</td>
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<tr>
<td>Diphenyl Hydantoin</td>
<td>400 mg</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>600 mg</td>
</tr>
<tr>
<td>Estrogen-Progesterone</td>
<td>800 mg</td>
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Fig. 4. Suppressive effects of various anti-arrhythmic agents on VPCs. None of the anti-arrhythmic agents proved effective. VPC tended to increase in frequency at the peri-ovulation period and almost disappeared during menstruation. After estrogene-progesterone administration, the VPCs were markedly decreased. Numbers indicate the severity of VPCs: 0: mean number of VPC/hr: < 5; 1: mean number of VPC/min: 1–5; 2: mean number of VPC/min: 6–10; 3: mean number of VPC/min: > 11; 4: occasional short run; 5: frequent short run. The dose of drugs showed the maximal total daily dose.
fist. A chest roentgenogram revealed no abnormalities of the heart or of the pulmonary vascular pattern. Hemograms, urinalysis, blood sugar, blood urea nitrogen, electrolytes and enzyme determinations were normal. An echocardiogram, phonocardiogram, and right and left heart catheterization revealed no abnormalities. Coronary cineangiography indicated no significant stenosis of the main coronary arteries. As shown in Fig. 3, myocardial biopsy of the right ventricular endocardium revealed that the myocardial tissues were surrounded by connective tissues and exhibited brown degeneration. These findings may be consistent with cardiomyopathy.

Suppressive drug treatment: As shown in Fig. 4, attempts to suppress the ectopic focus with various anti-arrhythmic agents such as Lidocaine, Disopyramide, Propranolol, Pindolol, Oxyphenolol, Diphenylhydantoin, and Ajmaline at various doses, singly or in combination, proved unsuccessful. In spite of continued drug therapy and fixed ventricular pacing at 90 beats/min, VT still recurrent (Fig. 5).

Continuous ECG monitoring apparently indicated that the VPCs tended to increase in frequency at the peri-ovulation period but almost disappeared during menstruation. An attempt was then made to induce non-ovulatory menstruation by the administration of contraceptive pills containing an estrogen-progesterone compound. The pills were administered for 20 consecutive days and then discontinued for the next 5 days, during which periods nonovulatory menstruation was induced. Administration of the pills was again begun on the day following the 5th day of discontinuation. As shown in Fig. 5, administration and discontinuation of the pills as described above apparently resulted in a marked reduction of the occurrence of VPCs and VT. After 3 months of observation, the patient was discharged on a regimen of the contraceptive agent in a condition relatively free from complaints, and she has remained under close observation in our out-patient clinic.

DISCUSSION

A large number of anti-arrhythmic drugs is now used clinically. The VPCs in the present patient, however, were quite refractory to virtually all of the anti-arrhythmic agents currently available in Japan. Quinidine and Procaïnamide were not used, because this patient showed hypersensitivity reactions to a small dose of these two drugs. Successful suppression of refractory tachycardia by transvenous rapid cardiac pacing has been reported by several investigators. However, we failed to suppress the VPCs in our patient with rapid cardiac pacing. So far as is known, this is the first report in English to describe a marked reduction in drug-resistant VPCs in a middle aged woman by using contraceptive pills containing an estrogen-progesterone compound. Furthermore, it is noteworthy that sudden 9 unexpected deaths had occurred in this patient's family. Although no autopsy data are available for these sudden unexpected deaths, it seems reasonable to speculate that all the deaths may have resulted from serious arrhythmia, judging from careful interviews with the relatives. It was repeatedly found in our patient's menstrual cycle that the occurrence of VPCs was most frequent at the peri-ovulation period, and thereafter decreased in frequency. It is not uncommon for VPCs to occur frequently in the premenstrual period or during menstruation. However, there seems to be no previous report indicating that VPC occurrence is apparently increased at around the ovulation period. Myocardial biopsy suggested the presence of some myocardial disorder. It seems probable
therefore that the myocardial disorder might provide a suitable situation for the occurrence of VPCs. Although a discussion of the mechanisms by which a sex hormone might alter the electrophysiological properties of myocardial tissues and induce VPCs is beyond the scope of the present paper, some such mechanism is presumably operative in the present case. It is generally recognized that a prolonged Q-T interval and frequent ventricular arrhythmia, not infrequently resulting in syncopal attacks, are observed in both the Jervell-Lange-Nielsen syndrome and the Romano-Ward syndrome: the former but not the latter involves a congenital deafness. However, Q-T prolongation has never been observed in the present case. Patients with mitral valve prolapse syndrome occasionally show frequent ventricular premature beats, which, though rarely, could lead to ventricular fibrillation and sudden death. The echocardiographic and phonocardiographic findings in our case are against the presence of mitral valve prolapse. Frequent occurrence of VPCs is commonly observed in patients with coronary artery disease, but the lack of evidence of coronary artery disease in coronary cineangiography militates against this being a likely explanation in our case. Serum electrolytes (K, Ca, Cl, Na, and Mg) remained within normal levels throughout her menstrual cycle. No essential changes in levels of serum electrolytes were observed even during the peri-ovulation period when VPCs occurred most frequently. Although the mechanism of the arrhythmic effect of the estrogen-progesterone remains to be elucidated, the present case report suggests that detailed surveys should be made to determine whether or not the occurrence of VPCs is increased at a certain period of the menstrual cycle and the occurrence of VPCs, the administration of a contraceptive agent containing estrogen-progesterone may represent an advisable procedure for possible therapy.

REFERENCES