Low-dose isoproterenol for repetitive ventricular arrhythmia in patients with Brugada syndrome


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Aims Arrhythmic storm or repetitive ventricular arrhythmia (VA) has been occasionally observed in Brugada syndrome (BS). A beta-adrenergic stimulator [isoproterenol (ISP)] has been reported to suppress this arrhythmic storm in sporadic cases. Accordingly, we investigated the antiarrhythmic effects of ISP infusion in consecutive BS patients with arrhythmic storm or repetitive VA.

Methods and results Seven BS patients with arrhythmic storm were studied. Intravenous ISP was administered as a bolus injection (1–2 μg), followed by continuous infusion (0.15 μg/min). Arrhythmic storm or repetitive VA was suppressed immediately after the bolus administration of ISP, which was followed by continuous infusion of low-dose ISP for 1–3 days. In all patients, ST-elevation decreased in right precordial leads. In six of the seven patients, VA subsided after the discontinuance of ISP. RR interval was shortened and ST-elevation in right precordial leads was decreased after ISP bolus injection. ST-elevation in right precordial leads remained decreased during continuous ISP infusion, whereas the RR interval returned to the control level.

Conclusion Continuous administration of low-dose ISP may be effective for the suppression of repetitive VA occurrence in patients with BS.

Keywords Isoproterenol; Brugada syndrome; Ventricular arrhythmia

Introduction

Brugada syndrome (BS) is characterized by ST-segment elevation in right precordial leads and nocturnal ventricular fibrillation (VF).1–3 These characteristics are modified by the autonomic nervous system.4 For example, vagal stimulation augments ST-elevation and induces ventricular arrhythmia (VA).5 In contrast, adrenergic beta stimulation attenuates ST-elevation and suppresses VA.6–8 Malignant VA is often observed in BS, but repetitive VA including electrical storm is a rare phenomenon in this syndrome. It has been reported that electrical storm in some cases of BS was suppressed by treatment with low-dose isoproterenol (ISP). However, there have been few systematic studies on short-term effects of low-dose ISP infusion in patients with BS who had repetitive VA or electrical storm. This study was, therefore, carried out to determine the short-term effects of beta-adrenergic stimulation on VA in BS patients with repetitive VA.

Methods

Patients

The subjects were seven consecutive patients who had been referred to our hospital between March 2000 and May 2005 for evaluation and treatment after detection of ECG abnormalities compatible with BS. The mean age of the subjects was 47 ± 9 years. All subjects had repetitive VA during or before admission. All patients had recurrent syncope episodes of unknown origin or had been resuscitated from cardiac arrest or VF. Only one case (no. 2) was a recurrent case, and all other cases were first attacks. Repetitive ventricular tachycardia (VT) occurred in one patient (no. 7). VF occurred during or before hospitalization in six patients (nos 1–6). All patients had several VF episodes or repetitive VT before ISP infusion. Genetic analysis of the SCN5A gene was performed in all patients. Three patients had SCN5A mutation (nos 3, 5, and 7) (Table 1). There were no patients of the same family. Electrolyte levels, metabolic status, and results obtained by cardiac imaging techniques, including echocardiography and right ventriculography, were normal in all patients. There were no apparent triggering factors (i.e. fever) of VA in any patient.

Criteria for diagnosis of BS

Brugada-type ECG was defined by the report of the second consensus conference.9 According to that report, there are three types (types 1–3) of repolarization pattern in Brugada-type ECGs. In this study, all patients showed Brugada-type 1 ECGs at least in one occurrence.
Patients who showed type 1 ECG only after a class I antiarrhythmic challenge test were not included. One patient (no. 4) showed type 2 ECG in a general condition in right precordial leads, but showed type 1 ECG immediately before a VF attack (Table 1).

Intravenous injection of ISP

ISP was administered to all patients when frequent VA occurred during or before hospitalization. ISP was administered as a bolus injection intravenously at a dose of 1–2 μg, followed by continuous infusion at a dose of 0.15–0.30 μg/min until the next day. When VA recurred after stopping administration of ISP the next day, ISP was re-administered for 2 more days. Twelve-lead ECG was recorded before and during administration of ISP, and RR, PQ, QRS, and QT intervals and ST-levels were evaluated. ST-levels were measured at J points in leads V1 and V2. The difference between ST-levels before and after administration of ISP was calculated.

Statistical analysis

Values are expressed as mean ± 1 SD. Statistical analysis was performed using Wilcoxon’s signed-rank test for paired values. A value of P less than 0.05 (two-sided) was considered statistically significant.

Results

VAs disappeared immediately after the bolus injection of ISP, followed by continuous injection in all patients (Figure 1). VA recurred in three patients when ISP administration was stopped the next day. ISP was re-administered for 2 more days in those patients. VA did not recur in two of those three patients when ISP administration was stopped on the fourth day. In the remaining one patient (no. 5), VF recurred when ISP administration was stopped on the fourth day. In this patient, 400 mg of oral quinidine sulphate was added to ISP injection and tapering of ISP was achieved. All patients felt transient palpitation after the initial injection of ISP, but no side effect was noted during the low-dose continuous administration of ISP.

RR interval was shortened and ST-elevation in leads V1 and V2 was decreased after ISP bolus injection. ST-elevation

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex/age</th>
<th>Family history of SCD</th>
<th>Type of VA</th>
<th>Number of repetitive VA episodes</th>
<th>Point of time of repetitive VA episodes</th>
<th>ST-morphology</th>
<th>SCNSA mutation</th>
<th>Induced VA by PES</th>
<th>Duration of ISP therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55/M</td>
<td>(−)</td>
<td>VF</td>
<td>Two times/24 h</td>
<td>Night</td>
<td>Type 1</td>
<td>No</td>
<td>(+)</td>
<td>24 h</td>
</tr>
<tr>
<td>2</td>
<td>55/M</td>
<td>(+)</td>
<td>VF</td>
<td>Three times/24 h</td>
<td>Early evening and morning</td>
<td>Type 1</td>
<td>No</td>
<td>(+)</td>
<td>72 h</td>
</tr>
<tr>
<td>3</td>
<td>33/M</td>
<td>(+)</td>
<td>VF</td>
<td>Three times/48 h</td>
<td>Early evening and night</td>
<td>Type 1</td>
<td>Yes</td>
<td>(+)</td>
<td>72 h</td>
</tr>
<tr>
<td>4</td>
<td>41/M</td>
<td>(−)</td>
<td>VF</td>
<td>Two times/48 h</td>
<td>Day time</td>
<td>Type 1(2)</td>
<td>No</td>
<td>(+)</td>
<td>24 h</td>
</tr>
<tr>
<td>5</td>
<td>47/M</td>
<td>(−)</td>
<td>VF</td>
<td>Two times/24 h</td>
<td>Night</td>
<td>Type 1</td>
<td>Yes</td>
<td>(−)</td>
<td>120 h + quinidine</td>
</tr>
<tr>
<td>6</td>
<td>59/M</td>
<td>(−)</td>
<td>VF</td>
<td>Two times/24 h</td>
<td>Early evening</td>
<td>Type 1</td>
<td>No</td>
<td>(−)</td>
<td>24 h</td>
</tr>
<tr>
<td>7</td>
<td>42/M</td>
<td>(+)</td>
<td>RpVT</td>
<td>Two times/24 h</td>
<td>Early evening</td>
<td>Type 1</td>
<td>Yes</td>
<td>(+)</td>
<td>24 h</td>
</tr>
</tbody>
</table>

RpVT, repetitive ventricular tachycardia; SCD, sudden cardiac death; (+), VF was induced by programmed electrical stimulation (PES); (−), VF was not induced by PES.

Figure 1 Occurrence of PVC and VF in case 5. (A) ECG before administration of ISP. PVC occurred, and QRS morphology of the PVC was left bundle branch block with inferior axis. (B) Onset of VF before ISP infusion. (C) Disappearance of PVC and VF after ISP infusion.
A clinical implication of low-dose continuous ISP

An implantable cardioverter defibrillator (ICD) is implanted in symptomatic patients with BS, especially those in whom VF has been detected. However, some patients have experienced an arrhythmic storm and frequent discharge from the ICD. It has been reported that some drugs (i.e., ISP and quinidine) or catheter ablation for premature ventricular contraction (PVC) is useful for the control of VF attack in such patients. However, catheter ablation may be difficult when PVC does not appear during the catheter session. Considering that many patients will be free after short periods of arrhythmic storm, temporary intravenous administration of ISP while arrhythmias occur might be useful in BS patients with repetitive VA.

In patients with BS, antiarrhythmic drug (class Ia or Ic) challenge tests have frequently unmasked and augmented typical ST-elevation. Intravenous pharmacological tests are, therefore, increasingly being performed worldwide to diagnose BS. However, repetitive VA is often induced by sodium channel blocker administration in patients with BS. We believe that ISP should be used as an emergency drug and administered immediately if VA occurs in a drug challenge test.

In the present study, we evaluated the effects of continuous administration of low-dose ISP for 1–3 days in seven consecutive patients with BS who had repetitive VA. We found that bolus injection of ISP suppressed VA in all patients and that the suppressive effects were maintained during continuous administration of ISP. The fact that six of the seven patients had no arrhythmia recurrence even after the termination of ISP administration for 3 days suggests that ISP might stabilize electrical activity within 3 days in a majority of patients with repetitive VA. When arrhythmic attack cannot be controlled by intravenous ISP therapy for 3 days, oral antiarrhythmic drugs should be considered. In our study, one patient in whom VF attack could not be controlled by intravenous ISP therapy for 3 days had no VF recurrence during continuous ISP infusion with an increased sympathetic nervous system activity. Miyazaki et al. reported that a beta-stimulant improved ST-elevation in some patients, and several case studies have shown the effectiveness of ISP in patients with BS.

Discussion

It is well known that the autonomic nervous system activity influences the occurrence of VA and ST-elevation in patients with BS. Increased vagal activity facilitates VA in patients with BS. Attacks of VF usually occur during the night while sleeping, and the evaluation of autonomic nervous system activity using RR variability showed an increased high-frequency component immediately before VF. Acetylcholine injection into the coronary artery increased ST-elevation in right precordial leads and induced VF in some patients. In contrast, increased sympathetic nervous system activity prevents VA. Miyazaki et al. reported that a beta-stimulant improved ST-elevation in some patients, and several case studies have shown the effectiveness of ISP in patients with BS.

Clinical implication of low-dose continuous ISP

Table 2 Electrocardiographic changes before and after ISP administration

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Electrocardiographic changes before and after ISP administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>PQ (s)</td>
<td>0.18 ± 0.01</td>
</tr>
<tr>
<td>QRS (s)</td>
<td>0.10 ± 0.02</td>
</tr>
<tr>
<td>QT (s)</td>
<td>0.37 ± 0.02</td>
</tr>
<tr>
<td>QTC (s)</td>
<td>0.40 ± 0.03</td>
</tr>
<tr>
<td>RR (s)</td>
<td>0.85 ± 0.10</td>
</tr>
<tr>
<td>ST(V1) (mV)</td>
<td>0.225 ± 0.094</td>
</tr>
<tr>
<td>ST(V2) (mV)</td>
<td>0.317 ± 0.093</td>
</tr>
</tbody>
</table>

Continuous parameters are expressed as mean ± SD.

in leads V1 and V2 remained decreased during continuous ISP infusion, whereas the RR interval returned to the control level (Table 2; Figure 2). Decreased ST-elevation in right precordial leads continued until discharge without any drugs in patients without recurrence of VA (Figure 3). However, in early recurrence cases, ST-elevation re-appeared immediately after the discontinuance of ISP infusion (Figure 4).

Repetitive VA recurred in two patients 1 month (no. 2) and 2 years (no. 3) after VA attack. Treatment with disopyramide at 300 mg/day was started in one patient (no. 2), and this patient has not experienced VA attack for 4 years with disopyramide.

SCN5A gene mutation did not influence the response to ISP therapy in this study.
not be controlled by ISP therapy for 3 days was administered oral quinidine sulphate for long-term control of arrhythmia. Interestingly, in four of the six patients who were discharged without any medications, there was no recurrence of VT/VF for a period of 2 years after ISP therapy for arrhythmic storm. This indicates that the duration of arrhythmic storm in BS is transient in a majority of patients with repetitive VA.

Considering that ST-level re-elevated after the discontinuance of ISP infusion in recurrent cases, the response of ST-elevation to ISP withdrawal might be a predictor of recurrence.

**Mechanism of the effectiveness of ISP**

Yan and Antzelevitch\(^{23}\) suggested that phase 2 re-entry is a mechanism of VA in patients with BS. Increased outward current or decreased inward current induces a change in the epicardial action potential, such as deepening of phase 1 notch and shortening of action potential duration, and excitation propagates as a difference in electrical voltage (phase 2 re-entry).\(^{24,25}\) Beta-adrenergic stimulation induces increased inward calcium current and attenuates the excess of outward current, resulting in action potential change. Interestingly, in our study, the decreased ST-level in right precordial leads and the suppressive effect of VA were maintained, even though heart rate had returned to the control level during low-dose ISP therapy. This suggests that increased heart rate is not an important factor in the therapeutic effects of ISP and that the direct effect of ISP on the myocardium to increase inward current is important for therapeutic effects in patients with BS. Thus, reduction of ST-elevation in right precordial leads might be an indicator for prevention of repetitive VA in patients with BS.
Study limitations
It is well known that ECG parameters for patients with BS vary greatly depending on the time of day. Because we evaluated ECG only once a day, the possibility that the ECG changes in our study were due to this characteristic cannot be ruled out.

Another limitation is the fact that our study is observational and it is, therefore, difficult to know whether the arrhythmia actually responded to ISP or settled spontaneously.

As adjustment of multiple comparison was not considered in the analysis, a careful interpretation was required.

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Conflict of interest: none declared.

References