Repetitive Sinoatrial Exit Block as the Major Mechanism of Drug-Provoked Long Sinus or Atrial Pause

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Prolonged sinus or atrial pause occurred in six patients with paroxysmal supraventricular tachycardia after drug administration. All six patients had normal sinus node function during control electrophysiologic study; the sinus cycle length ranged from 310 to 900 ms (mean 743 ± 141) and the longest sinus node recovery time ranged from 800 to 1,230 ms (mean 1,018 ± 168). A long sinus or atrial pause occurring at the termination of tachycardia or cessation of atrial pacing, ranging from 3,100 to 8,200 ms (mean 6,270 ± 1,674), was provoked by the administration of various drugs. These included an intravenous bolus injection of adenosine triphosphate (5 mg; one patient), intravenous bolus injection of verapamil (5 mg; one patient), a combination of a single oral dose of diltiazem (120 mg) and propranolol (20 to 40 mg; three patients), oral diltiazem (240 mg/day; one patient) and a combination of oral diltiazem (240 mg/day) and propranolol (160 mg/day; one patient).

Termination of an acute episode of paroxysmal supraventricular tachycardia frequently requires parenteral drug administration, whereas prevention of recurrence of paroxysmal supraventricular tachycardia usually requires long-term oral drug administration (1,2). Although parenteral and long-term oral drug administration are safe, they may occasionally cause syncope as a result of prolonged sinus or atrial pauses (3–8). The mechanism of a drug-provoked long sinus or atrial pause is unclear. In this study, we investigated the mechanisms of drug-provoked sinus or atrial pauses using a sinus node electrogram recording in a group of patients with paroxysmal supraventricular tachycardia in whom a long sinus or atrial pause was provoked by drug administration.

In five patients, low frequency deflections suggestive of sinus node activity with a cycle length between 620 and 3,500 ms were recorded during pauses. These findings suggest that repetitive sinoatrial exit block was responsible for the pause. Sinus slowing with a long arrest suggesting suppression of sinus automaticity was also noted in three of these five patients; the longest sinus arrest in these three patients was 4,160, 4,500 and >4,910 ms, respectively. The remaining patient with a pause of 6,840 ms had no recordable sinus activity, either reflecting suppression of sinus automaticity or technical failure.

In conclusion, this study suggests that both sinoatrial exit block and suppression of sinus automaticity are mechanisms for drug-provoked long sinus or atrial pauses.

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Methods

Study patients. Criteria for inclusion of patients in this study were 1) induction of sustained tachycardia in patients with clinically documented paroxysmal supraventricular tachycardia; 2) normal sinus node function during control electrophysiologic study; and 3) provocation of a prolonged sinus or atrial pause, defined as an interval >3 s after parenteral or oral drug administration. From September 1986 to December 1989, a total of 121 consecutive patients with sustained paroxysmal supraventricular tachycardia were prospectively studied. Six of the 121 patients developed a prolonged sinus or atrial pause after drug administration. There were five women and one man, aged 46 to 62 years (mean ± SD 56 ± 6). None had demonstrable organic heart disease.

Electrophysiologic study. The study protocol was approved by the Hospital Research Ethics Committee and written informed consent was obtained from all subjects. Electrophysiologic study was performed with patients in a postabsorptive nonsedated state. All cardiac medication was discontinued ≥72 h (or 5 plasma half-lives) before study. Multiple electrode catheters were positioned in the high right atrium, coronary sinus, right ventricular apex and across the tricuspid valve for recording of intracardiac electrograms and pacing from different sites of the heart. Surface electro-
Table 1. Clinical, Electrocardiographic and Electrophysiologic Characteristics of Six Patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Duration of SVT</th>
<th>Mechanism of SVT</th>
<th>Longest Sinus Arrest (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59 F</td>
<td>-</td>
<td>4</td>
<td>AVRT</td>
<td>800</td>
</tr>
<tr>
<td>2</td>
<td>52 F</td>
<td>-</td>
<td>2</td>
<td>AVRT</td>
<td>1,000</td>
</tr>
<tr>
<td>3</td>
<td>58 F</td>
<td>-</td>
<td>10</td>
<td>AVRT</td>
<td>1,200</td>
</tr>
<tr>
<td>4</td>
<td>46 F</td>
<td>-</td>
<td>13</td>
<td>AVRT</td>
<td>1,000</td>
</tr>
<tr>
<td>5</td>
<td>61 M</td>
<td>-</td>
<td>4</td>
<td>AVRT</td>
<td>1,170</td>
</tr>
<tr>
<td>6</td>
<td>67 F</td>
<td>-</td>
<td>20</td>
<td>AVRT</td>
<td>960</td>
</tr>
</tbody>
</table>

AVNRT = atrioventricular node reentrant tachycardia; AVRT = atrioventricular reentrant tachycardia; F = female; M = male; PP = sinus cycle length; IPP interval; SNRT = sinus node recovery time; SVT = supraventricular tachycardia.

Drug therapy for induced supraventricular tachycardia. After the control study, sustained supraventricular tachycardia was induced. Adenosine triphosphate (5 to 15 mg) was given intravenously as a bolus injection and the patient was monitored continuously with recording of the sinus node electrograms. Ten to 20 min later, a second dose of adenosine triphosphate was administered to reconfirm the effects. After this, verapamil (5 to 10 mg) was administered intravenously during an induced episode of sustained supraventricular tachycardia while the patient was monitored continuously. This concluded the initial study. All electrode catheters were removed; a hexapolar electrode catheter was introduced through the right antecubital vein, advanced to the right ventricular apex and secured for subsequent electrophysiologic studies.

The following drugs were tested sequentially on separate days: a single oral dose of combined diltiazem (90 to 120 mg) and propranolol (20 to 80 mg); diltiazem (240 mg/day in four divided doses); verapamil (320 mg/day in four divided doses); quinidine sulfate (1,600 mg/day in four divided doses); propranolol (400 mg/day in four divided doses); disopyramide phosphate (800 mg/day in four divided doses); propranolol (160 mg/day in four divided doses); a combination of diltiazem (240 mg/day in four divided doses) and propranolol (160 mg/day in four divided doses); digoxin (1.75 mg over a period of 24 h); and a combination of propranolol (160 mg/day in four divided doses) and digoxin (0.25 mg/day after a loading dose of 1.75 mg). When a prolonged atrial pause (≥3 s) that occurred at termination of tachycardia or cessation of rapid atrial pacing was noted during the studies, a sinus node electrogram was recorded either by the four proximal electrodes (interelectrode distance of 1 cm) of the hexapolar electrode catheter (three patients) or by a newly introduced quadripolar electrode catheter if the hexapolar electrode catheter was unable to record a sinus node electrogram (three patients).

Table 2. Drug-Provoked Long Sinus or Atrial Pause in Six Patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Drugs</th>
<th>Baseline Rhythm</th>
<th>Longest Pause (ms)</th>
<th>No. of SAB</th>
<th>CL of Sinus Electrogram</th>
<th>Longest Sinus Arrest (ms)</th>
<th>First Returning Beat</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ATP 5 mg IV</td>
<td>Sinoatrial</td>
<td>1,100</td>
<td>1</td>
<td>—</td>
<td>4,100</td>
<td>Sinus</td>
</tr>
<tr>
<td>2</td>
<td>DZ, 240 mg/day + Pro, 150 mg/day</td>
<td>JER</td>
<td>7,500</td>
<td>4</td>
<td>620-1,400</td>
<td>—</td>
<td>Sinus</td>
</tr>
<tr>
<td>3</td>
<td>Single dose of DZ, 120 mg + Pro, 40 mg</td>
<td>JER</td>
<td>8,200</td>
<td>3</td>
<td>1,060-3,300</td>
<td>4,800</td>
<td>Atrial or junctional</td>
</tr>
<tr>
<td>4</td>
<td>Single dose of DZ, 120 mg + Pro, 40 mg</td>
<td>Type 1 SAB and 2 1 SAB</td>
<td>6,100</td>
<td>5</td>
<td>640-1,100</td>
<td>—</td>
<td>Sinus</td>
</tr>
<tr>
<td>5</td>
<td>Verapamil, 5 mg IV</td>
<td>590-720</td>
<td>5,700</td>
<td>2</td>
<td>—</td>
<td>&gt;4,410</td>
<td>Atrial or junctional</td>
</tr>
<tr>
<td>6</td>
<td>DZ, 240 mg/day</td>
<td>780</td>
<td>6,840</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Junctional</td>
</tr>
</tbody>
</table>

ATP = adenosine triphosphate; CL = cycle length; DZ = diltiazem; IV = intravenous; JER = junctional escape rhythm; Pro = propranolol; SAB = sinoatrial exit block; SACT = sinoatrial conduction time.
Validation of sinus node electrogram. The sinus node electrogram was validated by recording of multiple repetitive, identical, low frequency deflections free of baseline drifting during an atrial pause that was noted on both the surface ECG and the high right atrial electrogram (9-14). These low frequency deflections were recorded only at the critical area of the junction of the superior vena cava and the right atrium. Moving the electrode catheter a few millimeters away from this area resulted in disappearance of these deflections. All measurements are presented as mean values ± SD.

Results

Clinical and ECG findings (Table 1). Although all six patients had recurrent palpitation, none had syncope during palpitation or after spontaneous termination of palpitation. In one patient (Case 5), two episodes of a prolonged atrial pause of 2.6 and 2.8 s, respectively, were noted after termination of supraventricular tachycardia after a single oral dose of diltiazem (120 mg) and after an intravenous bolus injection of verapamil (4 mg) in the emergency room. The sinus cycle length at rest in these six patients ranged from 680 to 1,000 ms (mean 833 ± 137). The QRS complexes were narrow in four of these six patients, intermittently pre-excited in one patient and persistently pre-excited in the remaining patient. The cycle length of clinically documented supraventricular tachycardia ranged from 300 to 400 ms (mean 343 ± 35).

Electrophysiologic studies (Table 1). During control study, the basic sinus cycle length ranged from 510 to 900 ms (mean 743 ± 141). The sinoatrial conduction time ranged from 50 to 100 ms (mean 80 ± 19). The longest sinus node recovery time ranged from 800 to 1,230 ms (mean 1,019 ± 160) and corrected sinus node recovery time ranged from 140 to 350 (mean 275 ± 86). Sustained supraventricular tachycardia was inducible in all six patients, including five with orthodromic AV reentrant tachycardia and one patient with slow-fast dual pathway AV node reentrant tachycardia. The induced tachycardia had a cycle length ranging from 260 to 400 ms (mean 358 ± 55). No patient had a prolonged atrial pause after electrical termination of tachycardia by overdrive pacing.

Drug provocation of prolonged atrial pause (Table 2). All six patients had a prolonged atrial pause at termination of supraventricular tachycardia or cessation of rapid atrial pacing after drug administration. The drugs that provoked a long atrial pause included adenosine triphosphate (5 mg by intravenous bolus injection) (Patient 1); combination of diltiazem (20 mg in a single oral dose) and propranolol (20 to 40 mg) (Patients 2 to 4); verapamil (5 mg by intravenous bolus injection) (Patient 5); a combination of diltiazem...
A prolonged atrial pause (duration 3,100 to 8,200 ms) was noted in all six patients after cessation of overdrive pacing or termination of supraventricular tachycardia. The paced cycle length was 220 ms and the pacing site was the coronary sinus (CS). Panel B shows a prolonged atrial pause due to a long sinus arrest of 4,160 ms after cessation of ventricular pacing with 1:1 retrograde ventriculoatrial conduction at a cycle length of 400 ms. The sinus arrest was followed by a sinus deflection (arrow) before subsequent ventricular pacing. Panel C shows an episode of prolonged atrial pause of 4,960 ms due to repetitive sinoatrial exit block (arrows) that occurred after cessation of rapid atrial pacing at a paced cycle length of 330 ms. The fifth sinus deflection is conducted with an atrial response. A, CS and V = low septal right atrial, coronary sinus and ventricular response to the basic rhythm or pacing; A, HRA, and V = low septal right atrial, coronary sinus and ventricular response to the induced supraventricular tachycardia; HBE, HBE, and HBE = His bundle, distal His bundle, and proximal His bundle electrograms; S = stimulus artifact. Other abbreviations as in Figure 1. The paper speed is 100 mm/s in panel A and 50 mm/s in panels B and C.

(240 mg/day orally) and propranolol (160 mg/day orally) (Patient 1) and diltiazem (240 mg/day orally) (Patient 6). Four patients (Patients 1 and 4 to 6) had sinus rhythm and two (Patients 2 and 3) had junctional rhythm with 1:1 retrograde conduction. Of the four patients with sinus rhythm, three had 1:1 sinoatrial conduction; their sinoatrial conduction time was 170, 210 and 140 ms, respectively. The other had intermittent type 1 and 2:1 sinoatrial exit block (Fig. 1).

A prolonged atrial pause (duration 3,100 to 8,200 ms [mean 6,270 ± 1,674]) was noted in all six patients after cessation of overdrive pacing or termination of supraventricular tachycardia. During the long atrial pause, low frequency deflections reflecting sinus activity and having a cycle length between 620 and 3,500 ms were observed in five patients (Patients 1 to 5; Fig. 2 to 5). Marked sinus slowing with a long arrest was also noted in three of these five patients; the longest sinus arrest in the three patients was 4,160, 4,800 and >4,910 ms, respectively (Fig. 2B, 6A and 6B). In the remaining patient (Patient 6), low frequency deflections were not recorded after a long sinus pause of 6,840 ms when junctional escape rhythm with 1:1 retrograde atrial conduction handcapped the recording of the sinus node electrograms. In the six patients, the first returning beat after the atrial pause was of sinus origin in two patients (Patients 1 and 4; Fig. 2C and 5C), junctional origin in two patients (Patients 2 and 6; Fig. 4B) and atrial or junctional, or both, in the remaining two patients (Patients 3 and 5; Fig. 3B and 6B).
Discussion

Syncope and paroxysmal supraventricular tachycardia. Paroxysmal supraventricular tachycardia is a benign clinical arrhythmia. The acute attack is frequently terminated by a simple vagal maneuver or parenteral drug administration; long-term prophylaxis is usually achieved by maintenance oral drug administration (1). Patients with paroxysmal supraventricular tachycardia may occasionally experience syncope at either the onset or the termination of an episode of tachycardia. The former results from hypotension due to a sudden decrease in stroke volume (15) or secondary to a vasovagal reflex triggered by tachycardia-induced catecholamine secretion (16). The latter results from a prolonged sinus or atrial pause at the termination of tachycardia, especially in patients with sick sinus syndrome (17).

Antiarrhythmic agents and sinus node function. Beta-adrenergic blockers, digitalis, calcium channel blockers, class I antiarrhythmic drugs and adenosine are known to depress sinus node function, causing sinus bradycardia, prolongation of sinus node recovery time and lengthening of sinoatrial conduction time (18-22). They are usually safe in clinical usage; symptomatic sinus node dysfunction occurs only rarely with acute parenteral administration or long-term oral administration of these agents. Nonetheless, cardiac asystole and a prolonged sinus or atrial pause have been described (3-8,23). Benaim (3) described a 57 year old man with supraventricular tachycardia taking practolol (600 mg/day) who developed cardiac asystole after intravenous administration of practolol (120 mg) and verapamil (7 mg). Tonkin et al. (4) observed marked prolongation of sinus node recovery time (4,040 ms) in a 70 year old patient with sick sinus syndrome and AV node reentrant tachycardia after intravenous administration of verapamil (0.15 mg/kg). Behnassen et al. (5) observed a 5 s sinus arrest after an intravenous bolus injection of adenosine in terminating AV reentrant tachycardia (5). DiMarco et al. (6) reported a 2 to 5 s sinus arrest after an intravenous bolus injection of
Figure 4. Case 2. Repetitive sinoatrial exit block resulting in a prolonged atrial pause after administration of a single oral dose of diltiazem (120 mg) and propranolol (40 mg). Panel A shows a sinus node recovery time of 860 ms after cessation of rapid atrial pacing at a paced cycle length of 360 ms before drug administration. Panel B shows a prolonged atrial pause of 4,680 ms due to repetitive sinoatrial exit block after cessation of ventricular pacing with 1:1 retrograde ventriculoatrial conduction at a paced cycle length of 400 ms after diltiazem and propranolol. The pause was followed by a junctional escape rhythm with 1:1 retrograde conduction. H = His bundle potential; other abbreviations as in Figures 1 and 2.

Adenosine in three patients with paroxysmal supraventricular tachycardia. Yeh et al. (7) observed severe sinus bradycardia with junctional escape rhythm in a patient after a single oral dose of a combination of diltiazem and propranolol was administered to terminate paroxysmal supraventricular tachycardia.

Kuo et al. (8) reported on a 27 year old woman with automatic atrial tachycardia and no previous sinus node dysfunction who developed a sinus pause of 8,920 ms 5 days after treatment with digoxin (0.25 mg/day), nadolol (80 mg/day) and amiodarone (1 g/day). A long sinus pause did not occur after discontinuation of drug therapy, but rechallenge with amiodarone caused prolonged cardiac asystole. Gould et al. (23) described a 77 year old woman who developed 2:1 sinoatrial exit block while taking tocainide (400 mg three times daily) for premature ventricular beats. These previously reported episodes in patients with drug-induced severe sinus depression usually occurred with pre-existing sinus node dysfunction. The six patients in the present study had no clinical evidence of sinus node dysfunction or a history of syncope. In five of these six patients, the long sinus pause occurred after oral drug administration.

Mechanisms of drug-provoked prolonged sinus or atrial pause. Several studies (11-14) have demonstrated that sinoatrial exit block rather than sinus node suppression is the major mechanism responsible for the abnormally prolonged sinus or atrial pause that occurs spontaneously after termination of supraventricular tachyarrhythmia, after rapid atrial pacing or during carotid sinus massage. In these cases, Mobitz type II or type I exit block with repetitive sinoatrial exit block is the mechanism of the prolonged pause (11-13). Complete sinoatrial exit block with atrial escape rhythm has also been shown (14) to be present in some patients with the bradycardia-tachycardia syndrome. Whether a similar mechanism is also responsible for the drug-provoked long sinus or atrial pause has not been clarified previously.
Figure 5. Case 4. Repetitive sinoatrial exit block resulting in a prolonged atrial pause after administration of a single oral dose of diltiazem (120 mg) and propranolol (40 mg). Panel A shows a sinus node recovery time of 1,000 ms after cessation of rapid atrial pacing at a paced cycle length of 330 ms before drug administration. Panels B and C are continuous recordings after diltiazem and propranolol, showing a prolonged atrial pause of 4,220 ms due to repetitive sinoatrial exit block (arrows) after cessation of ventricular pacing with 1:1 retrograde ventriculoatrial conduction at a paced cycle length of 400 ms. The last sinus deflection is conducted with an atrial response. Abbreviations as in Figures 1 and 2.

The present study demonstrates that repetitive sinoatrial exit block is the major mechanism responsible for the drug-provoked long sinus or atrial pause in patients without evidence of previous sinus node dysfunction. However, it is usually accompanied by suppression of sinus automaticity with sinus arrest. Sinoatrial exit block was documented in five of the six patients with a recordable sinus node electrogram, whereas slowing of sinus automaticity with a long sinus arrest was noted in three of these five patients. In the remaining patient with no recordable sinus node electrogram during a long pause, inability to record the sinus node electrogram could reflect either suppression of sinus automaticity or technical failure.

Clinical implications. This study has several clinical implications. First, both sinoatrial exit block and suppression of sinus automaticity are mechanisms of a drug-provoked long sinus or atrial pause in patients with paroxysmal supraventricular tachycardia without previous sick sinus syndrome. However, sinoatrial exit block appears to be the major mechanism. Second, a long sinus or atrial pause could be the mechanism of syncope in patients with paroxysmal supraventricular tachycardia when the combination of a beta-blocker and a calcium channel blocker is administered. Third, a long sinus or atrial pause could be a potential mechanism of syncope in patients with coronary artery disease when the patient is treated with the combination of a
beta-blocker and a calcium channel blocker. This may occur particularly if the patient has paroxysmal supraventricular tachyarrhythmias such as atrial fibrillation or flutter.

References


