Clinical Background

It is also of interest that the clinical background of both patients is so similar. Both had severe rheumatic valvular heart disease with significant tricuspid insufficiency. Whether such hemodynamic defects produce mechanical changes in the atria and also result in electrical alterations can only be speculated.

Acknowledgment

The authors thank Walter Judson, M.D., for referring case 2 and Michael Lapp, M.D. for help during the study of case 2.

References


Effects of Cycle Length on Atrial Vulnerability

CHRISTOPHER R. C. WYNHDIAM, M.B., FERNANDO AMAT-Y-LEON, M.D., DELON WU, M.D., PABLO DEnES, M.D., RAMESH DHINGRA, M.D., ROSS SIMPSON, M.D., AND KENNETH M. ROSEN, M.D.

SUMMARY The effect of cycle length on atrial vulnerability was studied in 14 patients manifesting reproducible repetitive atrial firing during atrial extra-stimulus (A2) testing. Repetitive atrial firing was defined as the occurrence of two or more premature atrial responses with return cycle (A1-A2) of 250 msec or less and subsequent mean cycle length of 300 msec or less, following A1. The zone of repetitive atrial firing could be defined in terms of its longest and shortest A1-A2 coupling intervals. Each patient was tested at a long cycle length (CL1) (mean 884 msec) and a short cycle length (CL2) (mean 557 msec). CL1 was sinus rhythm, and CL2 an atrial paced rhythm. Repetitive atrial firing occurred in two patients at CL1, and in all patients at CL2. Of the former two patients (group 2), the zone of repetitive atrial firing was markedly widened in one at CL1 due to a shortening of atrial functional refractory period (FRP) at CL2. In the other, zone of repetitive atrial firing could not be totally defined due to induction of sustained atrial flutter preventing definition of atrial FRP. The occurrence of repetitive atrial firing at only CL2 in 12 patients (group 1) reflected: 1) a shortening of atrial FRP from 294 ± 11 msec at CL1 to 242 ± 10 msec at CL2 (mean ± SEM; P < 0.01), allowing delivery of A2 at shorter coupling intervals (9); 2) the new occurrence of repetitive atrial firing at A1-A2 coupling intervals achievable at both cycle lengths (1); or 3) both effects (2).

In conclusion, decrease of cycle length potentiated atrial vulnerability. This demonstration implies that atrial pacing could potentiate occurrence of paroxysmal atrial fibrillation or flutter.

NONUNIFORM RECOVERY OF VENTRICULAR MUSCLE (dispersal of ventricular refractoriness) predisposes to ventricular fibrillation. Classically, cycle length has been said to affect uniformity of refractoriness, long cycle lengths causing variation in ventricular refractory periods, and short cycle lengths producing more uniform repolarization.1 It has been reported that long cycle lengths predispose to ventricular ectopic activity and ventricular fibrillation.2, 3

It has recently been suggested that slow atrial rates predispose to atrial ectopic activity by a similar mechanism.4 If this hypothesis were true, then one would expect shortening of atrial cycle length to decrease atrial vulnerability to atrial fibrillation. In the present study we examine the effects of atrial cycle length on the phenomenon of atrial extra-stimulus induced atrial repetitive firing. The results demonstrated that decreasing cycle lengths predisposed the atrium...
to repetitive firing. These results are relevant to the utilization of atrial pacing for the control of atrial dysrhythmia.

**Methods and Definitions**

Electrophysiologic studies were performed in our laboratories for evaluation of atrioventricular and intraventricular conduction defects, sinus node disease, and for elucidation of paroxysmal supraventricular and ventricular tachycardias. Electrophysiological evaluation includes determination of basic conduction intervals, incremental high right atrial and ventricular pacing and atrial and ventricular extrastimulus testing at two or more cycle lengths in most patients. P-A interval, as previously defined, is a measure of high-to-low right atrial conduction time. Sinus recovery time (SRT) is a mean of three determinations of the atrial asystolic period following sudden cessation of atrial pacing at 130 beats/min. Calculated sinoatrial time (SACT) is determined by the extrastimulus method of Strauss et al. Atrial functional refractory period (FRP) has been previously defined.

The following extrastimulus conventions were used in the present study: A1 was the designation for atrial electrograms of sinus or driven beats. A1-A2 was thus the cycle length of sinus rhythm or an atrial driven rhythm. S was the stimulus of driven beats (S-S1 being the driven cycle length). S2 and A2 were the extrastimulus and its high right atrial response, S2-S3 being the extrastimulus and A1-A2 the atrial coupling intervals. A3 was the first return beat following S2 and A4 was the second return beat.

Repetitive atrial firing (RAF) was defined during extrastimulus testing and was the occurrence of two or more early atrial responses with a return cycle (A1-A2) of 250 msec or less and a subsequent cycle length (A1-A4 in subsequent cycles) of 300 msec or less. The sequence of atrial activation was assessed from two or more right atrial catheter recording sites and sometimes a left atrial recording site. The surface cardiogram was inspected for P wave morphology during repetitive atrial firing and for evidence of atrial flutter or fibrillation.

The zone of RAF was defined as a zone of A1-A2 coupling intervals between the longest and shortest coupling intervals giving rise to RAF. Where reproducible RAF was induced at only a single coupling interval, the zone of RAF was expressed as one msec. The range of intervals is shown together with the total duration of the zone in cases where RAF was induced within a range of coupling intervals.

**Patient Selection**

Patients in this study were obtained by examination of recordings of all patients undergoing atrial extrastimulus testing in our laboratory. To be included in this study, patients had to have a reproducible zone of RAF, demonstrated at least one cycle length. Patients were included only if extrastimulus testing was performed at two cycle lengths, so that the effect of cycle length on RAF could be examined. The long cycle length tested was always designated as CL1, and the short CL as CL2. CL1 was sinus rhythm.

**Results**

Fourteen patients met the criteria for inclusion in the study. Table 1 lists the clinical and electrocardiographic features of the study group, which consisted of 11 males and three females, whose ages ranged from 26 to 84 (mean 60.1) years. Nine patients had diagnosable organic heart disease. Documented supraventricular arrhythmias occurred prior to the electrophysiologic study in six of the 14 patients. In one who had symptomatic sinus node disease, paroxysmal atrial flutter was documented. Electrophysiologic studies were performed for the purposes of prospective evaluation of bifascicular block in eight patients, for evaluation of sinus node disease in three patients, for known or suspected arrhythmia in two patients, and as part of an evaluation of the effects on conduction in aortic stenosis in one patient. Additional electrocardiographic and electrophysiologic data is presented in table 2. Heart rate at the time of study varied from 47–102 (mean 70.5) beats/min. Left atrial enlargement was present by ECG in six patients, but no cor-

---

**Table 1. Clinical Data**

<table>
<thead>
<tr>
<th>No./Age/Sex</th>
<th>Cardiac Diagnosis</th>
<th>Observed Arrhythmia</th>
<th>Reason for Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/63/F</td>
<td>HCVD</td>
<td>APB, SAB, PAT</td>
<td>RBBB, RAD</td>
</tr>
<tr>
<td>2/50/M</td>
<td>HCVD</td>
<td>—</td>
<td>Alternating BBB</td>
</tr>
<tr>
<td>3/65/M</td>
<td>HCVD</td>
<td>APB</td>
<td>RBBB, LASH</td>
</tr>
<tr>
<td>4/65/M</td>
<td>HCVD</td>
<td>—</td>
<td>LBBB</td>
</tr>
<tr>
<td>5/59/M</td>
<td>SSND</td>
<td>SB, P, ST</td>
<td>SSND</td>
</tr>
<tr>
<td>6/79/M</td>
<td>HCVD</td>
<td>SB, PAT</td>
<td>RBBB, RAD</td>
</tr>
<tr>
<td>7/28/M</td>
<td>HCVD</td>
<td>—</td>
<td>Suspected AS</td>
</tr>
<tr>
<td>8/44/M</td>
<td>PCD</td>
<td>—</td>
<td>RBBB, LASH</td>
</tr>
<tr>
<td>9/72/F</td>
<td>ASHD</td>
<td>—</td>
<td>RBBB, RAD</td>
</tr>
<tr>
<td>10/80/M</td>
<td>PCD</td>
<td>—</td>
<td>RBBB, LASH</td>
</tr>
<tr>
<td>11/84/M</td>
<td>SSND</td>
<td>SB, APB, PAFL</td>
<td>SSND</td>
</tr>
<tr>
<td>12/62/M</td>
<td>PDM</td>
<td>VT</td>
<td>LBBB, VT</td>
</tr>
<tr>
<td>13/60/M</td>
<td>SSND</td>
<td>SB, APB</td>
<td>SSND</td>
</tr>
<tr>
<td>14/33/F</td>
<td>VHD, M Ins.</td>
<td>—</td>
<td>Palpitations</td>
</tr>
</tbody>
</table>

Abbreviations: HCVD = hypertensive cardiovascular disease; SSND = symptomatic sinus node disease; PCD = primary conduction disease; ASHD = arteriosclerotic heart disease; VHD = valvular heart disease; M Insuf. = mitral insufficiency; APB = atrial premature beat; SAB = sinoatrial block; PAT = paroxysmal atrial reentrant tachycardia; SB = sinus bradycardia; T = paroxysmal atrial tachycardia; RBBB = right bundle branch block; RAD = right axis deviation; LASH = left anterior superior hemiblock; LBBB = left bundle branch block; AS = aortic stenosis.

**Table 2. Electrophysiologic Data**

<table>
<thead>
<tr>
<th>No.</th>
<th>Heart Rate (bpm)</th>
<th>P-A (msec)</th>
<th>SRT (msec)</th>
<th>SACT (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>24</td>
<td>980</td>
<td>&gt;195*</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>57</td>
<td>1080</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>49</td>
<td>870</td>
<td>120</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>32</td>
<td>1120</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>40</td>
<td>1110</td>
<td>150</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>42</td>
<td>760</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>102</td>
<td>20</td>
<td>900</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>30</td>
<td>990</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>68</td>
<td>38</td>
<td>1200</td>
<td>130</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>45</td>
<td>1140</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>64</td>
<td>58</td>
<td>1120</td>
<td>225</td>
</tr>
<tr>
<td>12</td>
<td>80</td>
<td>50</td>
<td>890</td>
<td>135</td>
</tr>
<tr>
<td>13</td>
<td>47</td>
<td>46</td>
<td>1080</td>
<td>102</td>
</tr>
<tr>
<td>14</td>
<td>92</td>
<td>33</td>
<td>650</td>
<td>—</td>
</tr>
</tbody>
</table>

Mean 70.5

Normal (mean ± 2 sd) 27 ± 18 998 ± 692 92 ± 60

*Patient #1 had a “zone 1” response to atrial extrastimulus testing extending 260 msec from atrial functional refractory period to end of cycle length, implying SACT not less than 195 msec.

Abbreviations: bpm = beats per minute; msec = milliseconds; P-A = P-A interval; SRT = Sinus recovery time; SACT = Sinoatrial conduction time.
relation with arrhythmias was found. P-A interval was prolonged in five patients. Sinus node recovery time was increased in no patient. Calculated sinoatrial conduction time was prolonged in two patients.

Repetitive Atrial Firing

In the group as a whole, mean CL₁ (sinus rhythm) was 884 msec and mean CL₂ (atrial paced rhythm) was 557 msec. Patients were grouped as follows: group 1 consisted of 12 patients in whom RAF was present only at CL₁. Group 2 consisted of two patients in whom RAF was present at both CL₁ and CL₂. No patient had RAF at only CL₁. Data are presented in tables 3 and 4 and summarized in figure 1.

Group 1 (table 3)

In group 1, CL₁ in the 12 patients was 870 ± 40 msec, and atrial functional refractory period was 292 ± 10 msec (mean ± SEM). Mean CL₂ was 565 ± 24 msec and mean atrial functional refractory period was 245 ± 9 msec. Atrial functional refractory periods at both CL₁ and CL₂ were within normal limits.

Repetitive atrial firing was noted only at CL₂. A zone of RAF with inner and outer limits could be defined in nine patients. The inner limit of the zone of RAF was within 10 msec of the atrial functional refractory period in every case, and ranged from 200 to 285 msec (mean, 236 ± 9). The outer limit of the zone of RAF in the nine patients ranged from 210 to 330 msec (mean, 266 ± 11 msec). The absolute duration of the zone of RAF ranged from 10 to 50 msec (mean, 30 ± 4 msec) in the nine patients in whom a definite zone could be defined. In the other three patients, RAF was limited to a single occurrence or multiple occurrences at the same coupling interval (zones are listed as one msec) (P < 0.01). Sustained (greater than two minutes) atrial fibrillation occurred in three patients. In one of these (4), this event precluded definition of the atrial functional refractory period.

Two effects accounted for the predominance of RAF at only CL₂ in group 1 patients. In 11 patients (1–11), atrial pacing (CL₂) shortened atrial functional refractory period from a mean of 294 ± 11 msec to 242 ± 10 msec. This allowed exposure of the atrium to close coupling intervals not previously tested at CL₁ (fig. 2). In one patient (12), there was no significant shortening of atrial functional refractory period. However, a zone of RAF was seen as a result of RAF occurring at coupling intervals which had been innocuous at CL₁, implying a potentiating effect of the shorter cycle length independent of the functional refractory period. In two patients (10 and 11), both effects appeared to contribute.

Group 2 (table 4)

Group 2 was composed of two patients with RAF at both CL₁ and CL₂. CL₂ in the two patients were 1280 and 660 msec respectively. CL₁ were atrial paced cycle lengths of 500 and 525 msec respectively. In patient 13, atrial functional

### Table 3. Repetitive Atrial Firing—Group 1

<table>
<thead>
<tr>
<th>Pt</th>
<th>CL₁</th>
<th>Presence of RAF</th>
<th>Atrial FRP</th>
<th>CL₂</th>
<th>Presence of RAF</th>
<th>Mean A³A³</th>
<th>Outer Limit</th>
<th>Inner Limit</th>
<th>Absolute Duration</th>
<th>Sustained A Fib</th>
<th>Atrial FRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>730</td>
<td>—</td>
<td>290</td>
<td>545</td>
<td>+</td>
<td>190</td>
<td>250</td>
<td>220</td>
<td>30</td>
<td>—</td>
<td>220</td>
</tr>
<tr>
<td>2</td>
<td>1030</td>
<td>—</td>
<td>280</td>
<td>667</td>
<td>+</td>
<td>220</td>
<td>240</td>
<td>220</td>
<td>20</td>
<td>—</td>
<td>220</td>
</tr>
<tr>
<td>3</td>
<td>750</td>
<td>—</td>
<td>280</td>
<td>667</td>
<td>+</td>
<td>205</td>
<td>270</td>
<td>245</td>
<td>25</td>
<td>—</td>
<td>235</td>
</tr>
<tr>
<td>4</td>
<td>1000</td>
<td>—</td>
<td>335</td>
<td>470</td>
<td>+</td>
<td>130</td>
<td>270</td>
<td>1</td>
<td>+</td>
<td>&lt;270*</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>870</td>
<td>—</td>
<td>280</td>
<td>500</td>
<td>+</td>
<td>135</td>
<td>260</td>
<td>210</td>
<td>50</td>
<td>—</td>
<td>200</td>
</tr>
<tr>
<td>6</td>
<td>980</td>
<td>—</td>
<td>305</td>
<td>600</td>
<td>+</td>
<td>210</td>
<td>300</td>
<td>1</td>
<td>—</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>330</td>
<td>—</td>
<td>280</td>
<td>450</td>
<td>+</td>
<td>225</td>
<td>210</td>
<td>200</td>
<td>10</td>
<td>—</td>
<td>200</td>
</tr>
<tr>
<td>8</td>
<td>930</td>
<td>—</td>
<td>360</td>
<td>667</td>
<td>+</td>
<td>260</td>
<td>330</td>
<td>285</td>
<td>45</td>
<td>—</td>
<td>285</td>
</tr>
<tr>
<td>9</td>
<td>880</td>
<td>—</td>
<td>320</td>
<td>500</td>
<td>+</td>
<td>195</td>
<td>290</td>
<td>250</td>
<td>40</td>
<td>—</td>
<td>250</td>
</tr>
<tr>
<td>10</td>
<td>1000</td>
<td>—</td>
<td>250</td>
<td>500</td>
<td>+</td>
<td>195</td>
<td>265</td>
<td>240</td>
<td>25</td>
<td>—</td>
<td>240</td>
</tr>
<tr>
<td>11</td>
<td>940</td>
<td>—</td>
<td>270</td>
<td>545</td>
<td>+</td>
<td>160</td>
<td>280</td>
<td>255</td>
<td>25</td>
<td>—</td>
<td>255</td>
</tr>
<tr>
<td>12</td>
<td>745</td>
<td>—</td>
<td>270</td>
<td>667</td>
<td>+</td>
<td>160</td>
<td>280</td>
<td>1</td>
<td>+</td>
<td>270</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>870</td>
<td>—</td>
<td>292</td>
<td>565</td>
<td>+</td>
<td>193</td>
<td>266</td>
<td>230</td>
<td>23</td>
<td>245</td>
<td></td>
</tr>
</tbody>
</table>

± SEM: ± 10 ± 24 ± 12 ± 11 ± 9 ± 5 = 9

*Atrial FRP not able to be determined due to sustained atrial fibrillation.

### Table 4. Repetitive Atrial Firing—Group 2

<table>
<thead>
<tr>
<th>Pt</th>
<th>CL₁</th>
<th>Presence of RAF</th>
<th>Mean A³A³</th>
<th>Outer Limit</th>
<th>Inner Limit</th>
<th>Absolute Duration</th>
<th>Sustained Atrial Flutter</th>
<th>Atrial FRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data at CL₁ (msec)</td>
<td>13</td>
<td>1280</td>
<td>+</td>
<td>120</td>
<td>390</td>
<td>1</td>
<td>—</td>
<td>390</td>
</tr>
<tr>
<td>14</td>
<td>660</td>
<td>+</td>
<td>250</td>
<td>230</td>
<td>215</td>
<td>35</td>
<td>+</td>
<td>&lt;215*</td>
</tr>
<tr>
<td>Data at CL₂ (msec)</td>
<td>13</td>
<td>500</td>
<td>+</td>
<td>120</td>
<td>320</td>
<td>240</td>
<td>80</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>525</td>
<td>+</td>
<td>190</td>
<td>230</td>
<td>230</td>
<td>1</td>
<td>+</td>
<td>&lt;230*</td>
</tr>
</tbody>
</table>

*Atrial FRP not able to be determined due to sustained atrial fibrillation or flutter.

Abbreviations: see table 3.
refractory period shortened from 390 to 240 msec, accounting for marked potentiation of RAF, from a single reproducible occurrence at CL₁ to a zone of 80 msec at CL₂. In patient 14, atrial functional refractory period could not be determined at either CL, due to the initiation of sustained atrial flutter. The effects of cycle length on zone of RAF could not therefore be determined in this patient. The outer limit of zone of RAF was a zone of sinoatrial echoes in both cases. The influence of cycle length upon zones of RAF in both groups is summarized in figure 1.

**Electrophysiological Characteristics of RAF**

The morphology of atrial activity on the surface electrocardiogram and on the intra-atrial electrograms was studied. Episodes of RAF of 10 beats or more were classified as atrial fibrillation if intra-atrial electrograms showed irregular depolarizations at a mean cycle length of 160 msec or less (fig. 3). Four patients (4,5,7,12) showed atrial fibrillation thus defined, in three of whom this was sustained (> two minutes duration). Atrial flutter was considered to be present when intra-atrial electrograms showed 10 or more regular depolarizations with a mean cycle length of about 200 msec. Three patients (9,10,14) showed atrial flutter thus defined; in one of these, this was sustained. Intra-atrial activation sequence could be defined in ten of the 14 patients; the remaining four had atrial fibrillation. The sequence during atrial flutter in patients 9, 10, and 14 was high to low in the right atrium in two patients, and low to high in the third. The remaining seven patients with RAF had a high to low right atrial sequence in six, and simultaneous high and low depolarization in one (1). Close inspection of the records did not reveal any episodes of dissimilar atrial rhythms occurring simultaneously in any patient.

**Other Observations**

In addition to RAF, the following atrial responses were seen with atrial extrastimulus testing. Definitions are as described by Dhingra et al. and all zones are in terms of the range of A₁A₂ coupling intervals producing each response.

At CL₁, nine patients had a zone of sinoatrial echoes (ZSE), five had a zone of sinus interpolation (ZI), and all except one patient (1) had a zone of sinus reset (ZR). The latter patient had only sinoatrial interference (zone one response) which extended to the sinus echo zone. All other patients in whom A₂ was delivered late in diastole also showed the usual zone of non-reset (ZNR) due to sinoatrial interference.

Sustained atrial arrhythmia after induction was defined as lasting longer than two minutes. In no case did this last longer than 24 hours, or necessitate cardioversion or drug therapy. One of the three cases (14) developing atrial flutter sustained this arrhythmia. None of the three had previously documented atrial flutter. Of the four patients developing
FIGURE 2.  Patient 3. Induction of repetitive atrial firing (RAF). Shown in each panel are standard leads I, II, III, and lead V1, two His bundle and low right atrial (HBE) and high right atrial (HRAE) electrograms. S1, S2, A1, A2, A3, A4, and A0 are respectively the driving and premature stimulus artifacts, the high right atrial electrograms of driven or sinus beats, the premature atrial test beat, the return beat, post-return beat and subsequent beats of RAF. Panel A (normal sinus rhythm [NSR], CL1 = 750 msec) shows A2 delivered outside the atrial functional refractory period (A1A2 of 280 msec) resulting in a sinoatrial echo. Panel B (atrial pacing, CL2 = 667 msec) shows A2 delivered at A1A2 of 270 msec defining the outer limit of zone of RAF. Panel C (CL2) shows the inner limit of zone of RAF defined by A1A2 of 245 msec near the atrial functional refractory period. Note the high-to-low right atrial activation sequence during RAF.
Figure 3. Patient 5. Induction of nonsustained atrial fibrillation. Shown in each panel are ECG leads I, II, III, VI, high right atrial (HRAE) and His bundle (HBE) electrograms. Panel A (normal sinus rhythm [NSR], CL1 = 900 msec) shows the functional refractory period as defined by A1A2 of 280 msec, where A2 interpolates. Panel A (atrial pacing [AP], CL2 = 500 msec) shows definition of outer limit of zone of RAF at A1A2 coupling interval of 260 msec, inducing atrial fibrillation as defined in text, with self-termination. Panel C defines the inner limit of zone of RAF at CL2 with an A1A2 interval of 210 msec. Total duration of zone of RAF is therefore 50 msec. This episode of atrial fibrillation terminated spontaneously 15 sec later. Conventions as for figure 2.
atrial fibrillation, three were sustained. In none of these four patients was atrial fibrillation previously documented.

**Discussion**

In the classic studies on ventricular vulnerability, it was demonstrated that ventricular fibrillation could be induced by a single suprathreshold ventricular extrastimulus. Various interventions are known to decrease ventricular fibrillation threshold (increase ventricular vulnerability). Sympathetic stimulation, ischemia, digitalis, and quinidine have been shown to bring this about by increasing the inhomogeneity of recovery. Further, ventricular fibrillation threshold was demonstrated to be reduced by long cycle lengths which increase dispersal of refractoriness. In keeping with these observations, Lown demonstrated that ventricular tachycardia complicating myocardial infarction was more common in patients with bradycardia than in those without. Recent work has challenged the classic teaching regarding cycle length and ventricular vulnerability. In a pooled series analyzed by the NIH team, mortality in myocardial infarction was less (12% of 346 patients) in the presence of untreated sinus bradycardia than (28% of 2012 patients) in the presence of heart rates above 60 beats/min. Ventricular fibrillation occurred with equal frequency (7%) in 735 patients following infarction, whether or not heart rate was below 60 beats/min. In the ischemic dog, atropine and cardiac pacing failed to reduce the incidence of "malignant ventricular arrhythmias." Furthermore, acceleration of rate in the ischemic dog actually decreased electrical stability and increased dispersal of refractoriness, an effect opposite to that classically found in the nonschematic dog. There is also some data demonstrating increasing dispersal of ventricular refractoriness at both very long and very short cycle lengths in the same experimental animal.

Less information is available regarding the atria, where data on the effects of cycle length upon atrial vulnerability is limited. Han et al. showed that at slow heart rates in the dog, there was greater dispersal of recovery of atrial excitability than at faster rates. Since ventricular ectopic activity was associated with temporal dispersal of refractoriness, it followed that atrial ectopic activity should also be increased at slow heart rates. Goel and Han subsequently described five patients in whom atrial ectopic activity associated with sinus bradycardia was abolished when the sinus rate increased spontaneously or after atropine. If, in man, shortening of the atrial cycle length increases dispersal of atrial refractory periods, one would predict that shortening cycle length with pacing would protect against atrial fibrillation and possibly other atrial dysrhythmias. On these grounds, atrial pacing has been suggested as prophylaxis in patients with known paroxysmal atrial fibrillation or flutter, particularly if complicating sinus node disease.

In this report we have examined the effects of cycle length on the induction of repetitive atrial firing, a marker of atrial vulnerability. Fourteen patients demonstrating repetitive atrial firing were tested at two cycle lengths. Twelve of the patients had RAF only at the shorter paced cycle length (CL2); two patients had RAF at both tested cycle lengths. Two effects accounted for the marked potentiation of RAF at CL2, namely, 1) a shortening of atrial functional refractory period (due to decrease in cycle length), allowing exposure of the atrium to shorter coupling intervals at CL2, and 2) a shift to the right (later in diastole) of the outer limit of the zone of RAF, by some effect not presently understood, of the paced cycle length itself. Sustained atrial flutter occurred in one patient and sustained atrial fibrillation in three others, none of whom had clinically documented arrhythmia prior to study. This result, namely the potentiation of atrial vulnerability at short cycle length, is contrary to what was expected from the previous animal and human work cited above. However, within the limitations of a comparison of our data in the human atria with Epstein's data in the ischemic canine ventricle, it would appear that the increase in vulnerability at shorter cycle lengths in both situations may partly be explained by the presence of organic disease of the myocardium.

As to the mechanism of repetitive atrial firing, it is interesting to note the high frequency with which sino-atrial echoes were seen in the present group of patients. Dhindra et al., examining patients without apparent sinus node disease utilizing atrial extra-stimulus technique, demonstrated sinus echo zones in only 11% of patients, as compared to 64% in the present series ($P < 0.001$). Sinus interposition was also more common in the present series as compared to Dhindra's series (34% vs. 19%, N.S.). The above findings imply that local areas of delay and reentry, as manifested by an increased incidence of sino-atrial echoes and interposition, are common in patients with demonstrable RAF. Whether RAF is due to reentrance in or around the sinus node, as suggested by Wu et al., in patients with sino-atrial reentrant tachycardia, is not answered by our results. The fact that high atrial electrograms preceded the low in most patients during RAF also suggests a site of reentry close to the stimulating electrode. If some other atrial stimulating site had been used in these studies, other sites of atrial reentry might have been more common.

Another note of caution should be entered regarding the present study. The possibility that we were demonstrating stimulated automaticity must be considered. Recent work suggests that cells depolarizing via slow calcium channels may develop after-depolarizations capable of achieving threshold, following extrastimuli. This phenomenon is potentiated by shortening of cycle length, as was repetitive atrial firing in the present study. It is also likely that atrial disease (presumably present in many of our patients) predisposes to utilization of slow channels, possibly by inactivating fast sodium channels. This also supports the possibility that our results could reflect cycle length potentiated slow channel automaticity.

**Clinical Implications**

We have demonstrated that decreasing cycle length promotes repetitive atrial firing and increased atrial vulnerability in man. The major clinical implication of these findings would be for the utilization of atrial pacing for increasing rates in sinus node disease and also for suppression of atrial premature beats or prophylaxis against paroxysmal atrial flutter or fibrillation. From our data, we would predict that atrial pacing could, or perhaps even should, potentiate the development of atrial fibrillation and/or flutter. This could be particularly troublesome in patients with symptomatic sinus node disease treated with atrial
pacing. However, if atrial pacing were to eliminate atrial premature beats, the potentiated vulnerability to RA F and atrial fibrillation would be insignificant.

It is interesting to speculate that cycle length potentiated atrial vulnerability in the form of RA F might be amenable to manipulation and control. Maneuvers or drugs which prolong CL and/or lengthen atrial functional refractory periods theoretically might narrow or abolish the zone of RA F. Such manipulations could be tested experimentally.

Our results suggest that the utilization of atrial pacing for prophylaxis against paroxysmal atrial flutter and fibrillation requires further investigation.

Acknowledgment

Appreciation is recorded of the expert help afforded by Loretta Kasparas, R.N., Richard Stein and Therese Molyneux.

References


Effects of cycle length on atrial vulnerability.
C R Wyndham, F Amat-y-Leon, D Wu, P Denes, R Dhingra, R Simpson and K M Rosen

doi: 10.1161/01.CIR.55.2.260

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/55/2/260

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/