Digitalis in the Pre-excitation Syndrome

Analysis during Atrial Fibrillation

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SUMMARY  The effect of digitalis in 21 patients with Wolff-Parkinson-White syndrome was analyzed with respect to the ventricular response during atrial fibrillation and antegrade and retrograde refractory periods of accessory pathways. Digitalis shortened the cycle length of the most rapid ventricular response (shortest R-R) (i.e., increased the ventricular response) in 6/21 patients, increased the cycle length in 7/21 patients, had no effect on the cycle length in 5/21, and could not be determined in 3/21. Digitalis could be directly related to the onset of ventricular fibrillation resulting from atrial fibrillation in 9/21 patients. Each of these patients had shortest R-R intervals (220 msec or less) during atrial fibrillation in the control state.

The results of this study indicate that no a priori prediction about the effect of digitalis on the antegrade conduction of accessory pathways can be made. By elective induction of atrial fibrillation it is possible to separate WPW patients into groups at high and low risk for developing ventricular fibrillation with the administration of digitalis.

RECENT DEVELOPMENTS in methods of preoperative and operative technique have established the potential role of surgical intervention for treatment of selected cases of the pre-excitation syndrome refractory to medical management.1, 2 The selection of optimal medical therapy has also been given a more rational basis by combining electrophysiologic studies with pharmacologic trials.3-11 The antegrade and retrograde effective refractory periods of normal and accessory pathways have potential prognostic importance and can be used to assess the value of various pharmacologic agents. It has been observed by several authors that there is an approximately linear relationship between the antegrade effective refractory period (AERP) of the accessory pathway (AP) and the maximal ventricular response during atrial fibrillation.12-16 However, refractory period determinations are frequently limited by atrial and ventricular muscle refractoriness. Additional information is provided by elective induction of atrial fibrillation before and after drug administration.

The use of digitalis in the treatment of pre-excitation syndrome has long been controversial.17-25 More recent electrophysiologic studies have suggested that digitalis may be contraindicated in some patients with Wolff-Parkinson-White syndrome; however, observations were limited to intravenous administration of ouabain and its effects on the refractory periods.6

The purpose of this study was to evaluate the use of refractory period determination and elective induction of atrial fibrillation to assess the effect of intravenous and oral digitalis therapy in patients with pre-excitation.

Materials and Methods

Twenty-one patients (13 male, 8 female) with the pre-excitation syndrome were selected who fell into either of two
categories: 1) those patients, generally with long antegrade refractory periods of the accessory pathway (AERPAP), who would not be endangered by the administration of digitalis, and 2) those patients with documented ventricular fibrillation following administration of digitalis during atrial fibrillation at an outside hospital. Their ages ranged from 13 to 68. All presented with recurrent tachyarrhythmias, some of which were life-threatening. Most were referred as potential candidates for surgical division of the AP. All studies were performed in the postabsorptive nonsedated state (except one) after informed consent was obtained. Antiarrhythmic therapy was discontinued at least 48 hours prior to the time of study. Under local anesthesia using sterile technique, two quadripolar electrode catheters for recording and stimulating were percutaneously introduced via the right femoral vein and advanced under fluoroscopic control to the apex of the right ventricle (RV) and the right atrium (RA) respectively. A third quadripolar electrode catheter was introduced via an antecubital vein, generally the left, and advanced to the coronary sinus (CS). A tripolar electrode catheter was also percutaneously introduced via the right femoral vein and positioned across the tricuspid valve to record a His bundle electrogram (HBE). Following introduction of all catheters, 100 units/kg of heparin were given intravenously. Standard ECG leads I and/or V1, and electrograms from the RV, the low lateral RA, the His bundle and the proximal and distal CS were recorded simultaneously and stored on magnetic tape at 3½ inches/second. Graphic records were obtained simultaneously at the time of study or at a later date by playback from tape onto a Mingograf 800 eight channel ink jet recorder at speeds of 100-200 mm/sec- ond. A simultaneous 10 msec time code was recorded with the data. Intracardiac electrograms were recorded at filter frequencies of 50 to 1000 Hz. Stimulation studies were performed with a specially designed stimulator* which delivered impulses of 2 msec duration at twice diastolic threshold. All electrical equipment was carefully grounded.

The antegrade and retrograde refractory periods of the normal and accessory pathways were determined using the extrastimulus technique.26 The methods used in the investiga-

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*Designed by Michael Feezor, Ph.D., and built by Philip Talbert.
tion of these patients have been described in detail elsewhere. 18-24-27

After control refractory periods were determined, atrial fibrillation was induced by pacing the RA or CS at cycle lengths of 150-200 msec if it did not occur spontaneously. Stimulation was begun using pulses of 2 msec duration delivered at twice diastolic threshold. If atrial fibrillation did not result, the pulse duration was gradually increased to 6 msec and the milliampere of the stimulus gradually increased. When pacing the CS, preliminary pacing at a slow rate was always done first to confirm the absence of left ventricular pacing through the wall of the coronary sinus. The shortest interval between two successive pre-excited beats was determined (as well as the average R-R interval determined over several minutes) were measured and compared to the antegrade ERP of the accessory pathway. Following completion of these control studies those patients in group 1 were given 0.75 mg-1.00 mg of digoxin i.v. Antegrade and retrograde refractory periods were repeated as was the induction of atrial fibrillation. At the end of the initial study, all catheters were removed with the exception of the CS catheter. The latter was frequently left in place to facilitate control of reciprocating tachycardia (RT). In seven of the 21 patients, the patient was returned to the ward and placed on oral digoxin 0.25 mg three times a day for two days then 0.25 mg maintenance dose per day until therapeutic blood levels were obtained. During this period, continuous telemetry to the coronary care unit was used to monitor cardiac rhythm. The patient was then completely re-studied in the same manner as in the control state.

Patients in group 2 were not given digoxin because documented ventricular fibrillation associated with administration of digitalis had occurred prior to admission to this institution. The ECG from the outside hospitals was analyzed and attempts were made to correlate this with electrophysiological data obtained during the control state. One patient in group 2 was referred with what proved to be irreversible hypoxic encephalopathy. She was not catheterized but was included because data in atrial fibrillation were available before and after the administration of digitalis.

Measurement of Serum Digoxin Levels

Digoxin serum levels were measured by standard Gamma-coat 1891 Digoxin Radioimmunoassay techniques. 28 Normal levels at this hospital range from 0.5-2.0 ng/ml with an accuracy of 0.3 ng/ml.

Blood levels were drawn at the conclusion of the electrophysiological studies when i.v. digoxin was used, and in the case of oral digoxin studies, the afternoon before the study to assure that the patient had a therapeutic level, then again immediately following the electrophysiological study. Blood levels were generally unavailable in group 2 patients, who were referred following cardiac arrest precipitated by administration of digitalis. These patients were therefore not rechallenged with the drug.

Complications

In our hands this method has met with little morbidity and no mortality. Thus in only four of 21 patients was DC cardioversion required to terminate atrial flutter-fibrillation.

Results

A total of 21 patients with Wolff-Parkinson-White syndrome underwent study. Clinical results are tabulated in table 1. Ten patients were referred with documented ventricular fibrillation (VF). Of these ten, nine developed VF while on digitalis and were subsequently not given any digitalis during the studies at this institution. One patient (TJ) who was referred for VF was on no drugs at the time of fibrillation, and this patient was given i.v. digoxin during the course of his study. The remaining 11 patients were referred for reciprocating tachycardia and/or spontaneous atrial flutter-fibrillation. Of these, nine were studied on i.v. digoxin while two were studied on oral digoxin. Of the nine studied on i.v. digoxin five also were restudied on oral digoxin. Atrial fibrillation was observed or induced in 20/21 patients in the control state. In one patient in whom atrial fibrillation could not be induced in the control state, atrial flutter occurred; however, with oral administration of digoxin atrial fibrillation was induced. The results are summarized in figure 1 and tabulated in table 2 and table 3.

Effect of Digoxin on the Ventricular Response (R-R interval) during Atrial Fibrillation

Group 1

Atrial fibrillation was induced in the control state and in the acutely digitalized state in 10/10 patients. The cycle length of the shortest pre-excited R-R interval (ventricular response) was decreased 20-65 msec (mean 45 msec) in 3/10 cases, increased 20-100 msec (mean 63 msec) in 6/10, and remained the same (± 10 msec) in 1/10. The average R-R interval paralleled the changes in the shortest R-R interval, with two exceptions. One patient with no change in the shortest R-R had a decrease of 80 msec in the cycle length of the average ventricular response. Another patient with a decrease in the shortest R-R interval had no change of the average R-R interval in i.v. digoxin.

Comparison of the results in the five patients receiving both i.v. and oral digoxin showed that it was impossible to predict the results of oral administration for either the shortest or average R-R intervals from the results of acute i.v. digoxin administration. The shortest R-R interval was noted to have the same directional trend in 3/5 cases, increasing 150 msec in one of these and decreasing 20-30 msec in two (fig. 2). In 2/5 cases there was a marked discrepancy between oral and i.v. digoxin. In one case i.v. digoxin increased the shortest R-R interval 50 msec. In the other case, there was no change (± 10 msec) with i.v. digoxin while oral digoxin increased the shortest R-R 45 msec. The average R-R interval changes with i.v. and oral digoxin did not correlate with either the changes in the shortest R-R nor the results of i.v. vs oral digoxin.

In the two patients studied on only chronic oral digoxin, one increased the shortest and average cycle length by 30 msec while the other had no inducible atrial fibrillation in the control state; however, it was readily induced on oral digoxin. The shortest pre-excited R-R interval during the atrial fibrillation was 230 msec while that seen during atrial flutter during the control state was 345 msec with an atrial rate of 150 msec.
### Table 1. Clinical Characteristics of Wolff-Parkinson-White Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>Site of AP</th>
<th>Age at Study</th>
<th>Sex</th>
<th>Referring Site of Ventricular Arrhythmia</th>
<th>Associated Cardiac Disease</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD</td>
<td>L</td>
<td>35</td>
<td>F</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>No arrhythmia</td>
</tr>
<tr>
<td>MF</td>
<td>S</td>
<td>29</td>
<td>M</td>
<td>RT</td>
<td>None</td>
<td>Propranolol</td>
<td>No arrhythmia</td>
</tr>
<tr>
<td>GG</td>
<td>R</td>
<td>32</td>
<td>M</td>
<td>RT; AF/F</td>
<td>Surgery</td>
<td>∆ gone - no arrhythmia</td>
<td></td>
</tr>
<tr>
<td>CH</td>
<td>L</td>
<td>49</td>
<td>M</td>
<td>RT; AF/F</td>
<td>CAD</td>
<td>Surgery</td>
<td>∆ gone - no arrhythmia</td>
</tr>
<tr>
<td>RW</td>
<td>L</td>
<td>57</td>
<td>M</td>
<td>rT</td>
<td>CAD</td>
<td>Digoxin</td>
<td>No arrhythmia</td>
</tr>
<tr>
<td>JJ</td>
<td>L</td>
<td>46</td>
<td>M</td>
<td>RT; AF/F</td>
<td>Surgery</td>
<td>∆ gone - no arrhythmia</td>
<td></td>
</tr>
<tr>
<td>LQ</td>
<td>L Retro +</td>
<td>13</td>
<td>M</td>
<td>RT</td>
<td>None</td>
<td>Propranolol</td>
<td>No arrhythmia</td>
</tr>
<tr>
<td>EB</td>
<td>S</td>
<td>32</td>
<td>F</td>
<td>RT</td>
<td>BMV</td>
<td>Digoxin</td>
<td>No arrhythmia</td>
</tr>
<tr>
<td>AC</td>
<td>L + EAVN</td>
<td>46</td>
<td>M</td>
<td>RT; AF/F</td>
<td>Surgery</td>
<td>∆ gone - no arrhythmia</td>
<td></td>
</tr>
<tr>
<td>KD</td>
<td>L</td>
<td>45</td>
<td>F</td>
<td>RT</td>
<td>None</td>
<td>Quinidine</td>
<td>No arrhythmia</td>
</tr>
<tr>
<td>TJ</td>
<td>Mahaim +</td>
<td>51</td>
<td>M</td>
<td>VF (no drug)</td>
<td>None</td>
<td>Quinidine</td>
<td>No arrhythmia</td>
</tr>
<tr>
<td>GM</td>
<td>R</td>
<td>26</td>
<td>M</td>
<td>RT; AF/F</td>
<td>None</td>
<td>Propranolol</td>
<td>No arrhythmia</td>
</tr>
</tbody>
</table>

**Group 1. Patients with no documented ventricular fibrillation on digitalis**

**Group 2. Patients with documented ventricular fibrillation while on digitalis**

**Abbreviations:** EAVN = enhanced A-V node; L = left free wall; R = right free wall; S = septal; Retro = accessory pathway with retrograde but no antegrade conduction; RT = reciprocating tachycardia; AF/F = atrial flutter-fibrillation; CAD = coronary artery disease; BMV = balloon mitral valve; ∆ = delta wave.

### Table 2. Effect of Digitalis on the Cycle Length of Ventricular Response during Atrial Fibrillation

<table>
<thead>
<tr>
<th>Pt</th>
<th>C (msec)</th>
<th>IV dig (msec)</th>
<th>PO dig (msec)</th>
<th>C (msec)</th>
<th>IV dig (msec)</th>
<th>PO dig (msec)</th>
<th>Digitalis Blood Dosage</th>
<th>Digitalis Blood Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>level</td>
<td>level</td>
</tr>
<tr>
<td>LD</td>
<td>350</td>
<td>500</td>
<td>420</td>
<td>530</td>
<td>1000</td>
<td>645</td>
<td>0.75 5.0</td>
<td>0.25 1.9</td>
</tr>
<tr>
<td>MF</td>
<td>250</td>
<td>220</td>
<td>215</td>
<td>290</td>
<td>322</td>
<td>323</td>
<td>0.75 4.4</td>
<td>0.25 1.6</td>
</tr>
<tr>
<td>GG</td>
<td>260</td>
<td>270</td>
<td>305</td>
<td>468</td>
<td>385</td>
<td>429</td>
<td>0.75 NA</td>
<td>0.25 0.6</td>
</tr>
<tr>
<td>CH</td>
<td>220</td>
<td>200</td>
<td>195</td>
<td>357</td>
<td>350</td>
<td>300</td>
<td>0.75 6.4</td>
<td>0.25 2.2</td>
</tr>
<tr>
<td>RW</td>
<td>350</td>
<td>300</td>
<td>300</td>
<td>467</td>
<td>600</td>
<td>349</td>
<td>0.75 1.2</td>
<td>0.25 1.3</td>
</tr>
<tr>
<td>JJ</td>
<td>Atrial flutter only @ 345</td>
<td>345</td>
<td></td>
<td>380</td>
<td>380</td>
<td>-</td>
<td>0.25 QD</td>
<td>0.25 1.9</td>
</tr>
<tr>
<td>LQ</td>
<td>230</td>
<td>260</td>
<td>-</td>
<td>300</td>
<td>-</td>
<td>333</td>
<td>-</td>
<td>0.25 QD</td>
</tr>
<tr>
<td>EB</td>
<td>240</td>
<td>340</td>
<td>-</td>
<td>312</td>
<td>402</td>
<td>-</td>
<td>1.0 6.0</td>
<td>-</td>
</tr>
<tr>
<td>AC</td>
<td>315</td>
<td>250</td>
<td>-</td>
<td>380</td>
<td>362</td>
<td>-</td>
<td>0.75 5.9</td>
<td>-</td>
</tr>
<tr>
<td>KD</td>
<td>300</td>
<td>320</td>
<td>-</td>
<td>375</td>
<td>449</td>
<td>-</td>
<td>0.75 0.6</td>
<td>-</td>
</tr>
<tr>
<td>TJ</td>
<td>205</td>
<td>240</td>
<td>-</td>
<td>283</td>
<td>290</td>
<td>-</td>
<td>1.0 10.8</td>
<td>-</td>
</tr>
<tr>
<td>GM</td>
<td>280</td>
<td>310</td>
<td>-</td>
<td>312</td>
<td>324</td>
<td>-</td>
<td>1.0 6.1</td>
<td>-</td>
</tr>
</tbody>
</table>
**Group 2**

There were nine patients with the pre-excitation syndrome referred to this institution who had documented ventricular fibrillation while on digitalis. Four of these patients were given i.v. digitalis at outside hospitals while having an attack of atrial fibrillation. In these cases, ECG monitoring was in progress during the time of acute digitalization which allowed documentation of the resulting VF and analysis of the ventricular response during AF while on digitalis. One such example is shown in figure 3. Analysis of these data was then compared to data obtained under control conditions in our laboratory during AF. Five of the nine patients experienced a near-lethal arrhythmia for the first time only after institution of chronic oral digoxin. In three of these five, records showing the transition of AF to VF were available for analysis while two were already in VF upon reaching the outside hospital. All of these patients were successfully resuscitated by ambulance crews or hospital emergency room staff and referred to this institution for evaluation. The time course relationship of the digitalization and resulting VF is summarized in table 3. In three patients given i.v. digitalis, the cycle length of the shortest pre-excited R-R interval was decreased 20 msec in one and was unchanged in two while the average cycle length was decreased 15-77 msec (mean 44 msec). In the three patients on chronic oral digitalis where records were adequate for analysis the shortest R-R interval decreased 20 msec in one (average decreased 20 msec) and remained the same in two (average decreased 65 msec in one, increased 25 msec in one). In the three patients where no adequate records exist, no comparison could be drawn between the control state and the digitalized state. It is significant to note that in each case where VF occurred, the shortest R-R interval observed in the control state was less than 220 msec. This has been observed previously by this institution in other WPW patients with VF.

### Effect of Digoxin on Antegrade and Retrograde Refractory Periods of Accessory Pathways

The effect of digoxin on the antegrade ERPAP and/or retrograde ERPAP could be exactly determined in only 6/21 patients because of atrial and/or ventricular muscle refractoriness. In 4/6 it was possible to measure the effect of digoxin on the antegrade ERPAP, increasing in one and no change in three. In 2/6 the effect of digoxin on the retrograde ERPAP was measurable, decreasing in one and with no effect on the other.

### Ventricular Fibrillation in the Setting of Enhanced Conduction in the A-V Node

Two patients with enhanced conduction in the A-V node in combination with a Mahaim fiber (fasciculo-ventricular connection) were encountered. This combination constitutes one of the pre-excitation syndromes.

In one (DG), VF occurred when intravenous digoxin was administered for atrial fibrillation with a rapid ventricular response. Prior to the onset of VF, the shortest R-R and the average R-R of the ventricular response decreased.

In the other patient (TJ), ventricular fibrillation spon-

---

**Table 3.**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NO DOCUMENTED VENTRICULAR FIBRILLATION - 11 PATIENTS</strong></td>
<td><strong>VENTRICULAR FIBRILLATION OUTSIDE DUMC - 10 PATIENTS</strong></td>
</tr>
<tr>
<td>2 patients - oral Dig</td>
<td>1 patient - VF on no medication</td>
</tr>
<tr>
<td>1/2 AF control and Dig</td>
<td>9 patients - VF on Dig</td>
</tr>
<tr>
<td>+ SRR (Ave 1)</td>
<td>1V Dig + SRR (Ave 1)</td>
</tr>
<tr>
<td></td>
<td>AF on control and Dig</td>
</tr>
<tr>
<td>1/2 AF flutter control, Dig</td>
<td>4 patients - 1V Dig</td>
</tr>
<tr>
<td>+ SRR (Ave 1)</td>
<td>1/4 + SRR (Ave 1)</td>
</tr>
<tr>
<td></td>
<td>1/4 + SRR (Ave 1)</td>
</tr>
<tr>
<td></td>
<td>6/10 + SRR (Ave 1)</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Summary of results of administration of digitalis in patients with the Wolff-Parkinson-White syndrome. DUMC = Duke University Medical Center; AF = atrial fibrillation; VF = ventricular fibrillation; SRR = shortest R-R interval.
Table 3. Effect of Digitalis on the Cycle Length of Ventricular Response during Atrial Fibrillation

<table>
<thead>
<tr>
<th>Pt</th>
<th>Shortest R-R (msec)</th>
<th>Average R-R (msec)</th>
<th>Dig Dose IV (mg)</th>
<th>Blood Level (ng/ml)</th>
<th>Duration of AF before VF</th>
<th>Relationship of digitalis therapy to onset of VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>JC</td>
<td>160 160 VF —</td>
<td>354 277 —</td>
<td>1.375 NA</td>
<td>—</td>
<td>—</td>
<td>14 hrs. Digoxin given over the course of 12½ hours prior to VF.</td>
</tr>
<tr>
<td>DE</td>
<td>190 200 VF —</td>
<td>325 310 —</td>
<td>—</td>
<td>0.5 NA</td>
<td>—</td>
<td>3-4 hrs. VF occurred 30 minutes after digoxin.</td>
</tr>
<tr>
<td>KH*</td>
<td>215* VF —</td>
<td>304* VF —</td>
<td>0.25 QD 0.68</td>
<td>—</td>
<td>—</td>
<td>10 min. On oral digoxin for 6 months, VF followed first and only episode of AF.</td>
</tr>
<tr>
<td>SH</td>
<td>150 160 VF —</td>
<td>175 200 —</td>
<td>—</td>
<td>0.25 QD NA</td>
<td>—</td>
<td>4-5 hrs. On oral digoxin, 3 episodes of AF resulted in VF. (Before digoxin, no VF occurred with AF.)</td>
</tr>
<tr>
<td>JM</td>
<td>185 VF —</td>
<td>260 —</td>
<td>—</td>
<td>0.25 QD NA</td>
<td>—</td>
<td>1 hr. On oral digoxin. (Before digoxin, had flutter with 1:1 @ 300/min.)</td>
</tr>
<tr>
<td>RR</td>
<td>180 160 VF —</td>
<td>215 195 —</td>
<td>—</td>
<td>0.25 QD NA</td>
<td>—</td>
<td>1 hr. On oral digoxin, VF followed first episode of AF since digitalization.</td>
</tr>
<tr>
<td>NS</td>
<td>180 160 VF —</td>
<td>280 240 —</td>
<td>1.6 mg Cedilanid</td>
<td>NA</td>
<td>—</td>
<td>6 hrs. VF occurred 45 minutes after Cedilanid.</td>
</tr>
<tr>
<td>DG</td>
<td>230 220 VF —</td>
<td>315 250 —</td>
<td>—</td>
<td>0.25 QD 0.6</td>
<td>—</td>
<td>9 hrs. On oral digoxin for 6 months, VF followed second episode of AF on digoxin.</td>
</tr>
<tr>
<td>SA</td>
<td>180 VF —</td>
<td>240 VF —</td>
<td>0.8 mg Cedilanid</td>
<td>NA</td>
<td>—</td>
<td>4 hrs. VF occurred 2 hours after i.v. Cedilanid.</td>
</tr>
</tbody>
</table>

*Under general anesthesia and 1.9 mg % quinidine.
NA = not available.

**Figure 2.** Effect of digitalis on the shortest R-R interval during atrial flutter-fibrillation. In panels A to C, tracings from above are standard ECG leads V1 and V5 and bipolar electrograms from the lateral right atrium (LRA) and the proximal (CS1) and distal (CS2) coronary sinus. Panel A: Atrial flutter-fibrillation is present in the control state giving the most rapid ventricular response (shortest R-R interval of 250 msec). Panel B: Atrial flutter-fibrillation present in the control state giving the most rapid ventricular response (shortest R-R interval of 250 msec). Panel C: Atrial flutter-fibrillation present in the control state giving the most rapid ventricular response (shortest R-R interval of 250 msec).
Patients with the pre-excitation syndrome are susceptible to two types of dysrhythmias: reciprocating tachycardia and atrial flutter-fibrillation with a rapid ventricular response resulting from antegrade conduction over the accessory pathway. In some patients these two dysrhythmias appear to be causally related, as evidenced by the occasional observation of reciprocating tachycardia spontaneously deteriorating into atrial fibrillation. In other patients, there appears to be a coincidence of a condition of recurring atrial fibrillation from whatever cause, and the presence of an accessory pathway. In either case, a life-threatening ventricular response and ventricular fibrillation may result during atrial flutter-fibrillation if the refractory period of the accessory pathway is short, due to rapid conduction across the pathway. This has been proposed as a possible cause of sudden death in patients with pre-excitation syndrome by Dreifus et al. The assessment of the effectiveness of a particular antiarrhythmic regime, aside from the clinical course, has been previously based largely on modification of the degree of pre-excitation and/or the ease of induction of reciprocating tachycardia and modification of the refractory periods of the accessory pathway. Frequently, the objective measurement of refractory periods is often limited by the refractoriness of atrial and/or ventricular muscle as noted from our results and those of others.

In our present studies, we attempted to examine objective measures of pharmacological effects in an attempt to elucidate the effect of digitalis in the pre-excitation syndrome and elucidate the predictive value of i.v. digoxin when oral digoxin therapy is contemplated. The antegrade refractory period of the accessory pathway gives only an indirect measure of what the fastest ventricular response during atrial fibrillation might be. The response of the ventricle during spontaneous or induced atrial fibrillation constitutes a more direct measure of the potential to sustain a life-threatening ventricular response and the effectiveness or ineffectiveness of any therapeutic measures. In some patients, sustained periods of concealed anomalous conduction into the accessory pathway may modify the rapidity of the ventricular response. However, in such patients, observation during atrial fibrillation over the course of several minutes will invariably unmask the potential of an accessory pathway to conduct rapidly.

The effect of digitalis on the pre-excitation syndrome was first noted by Scherf and Schönbrunner, in a more detailed study, noted that in some WPW patients, digitalis enhanced pre-excitation. In the ensuing years, the place of digitalis in the treatment of the pre-excitation syndrome has remained highly controversial, with some authors emphasizing that digitalis at times converts atrial fibrillation in the pre-excitation syndrome. Digitalis has long been used successfully with impunity in the pediatric age group for the treatment of tachyarrhythmias associated with pre-excitation. However, unlike the adult patient, the pediatric patient rarely, if ever, suffers from atrial fibrillation, and therefore minimal risk would appear to be associated with the use of digitalis in children. The adult patient, conversely, is indeed at risk for developing atrial fibrillation as he becomes older. Wells and Durrer have emphasized the potential danger of intravenous digitalis in patients whose accessory pathways have short refractory periods. In an earlier communication, we made a preliminary statement that oral digoxin appeared to have little or no effect on the ventricular response during atrial fibrillation in the pre-excitation syndrome. Based on our present study, we must now conclude that the effect of digoxin cannot be predicted a priori as evidenced by the fact that approximately one-third of the patients had an increase in ventricular response rate during atrial fibrillation, approximately one-third decreased their response rate, while the remaining third were unaffected.

The fact that digoxin can decrease the AERPAP and hence increase the ventricular response rate makes it a potentially lethal drug in the setting of an already rapidly conducting accessory pathway. This was evidenced by the fact that in those patients with the shortest R-R intervals of 220 msec or less, administration of digitalis was associated with ventricular fibrillation in 9/21 patients. Prior to administration of digitalis, none of these patients had ventricular fibrillation associated with atrial fibrillation.

The fact remains that some patients with the pre-excitation syndrome have received digoxin in the past for this
tachyarrhythmia with actual cessation of the atrial fibrillation rather than suffering a lethal deterioration due to ventricular fibrillation. Because of the documented ability of digitalis to increase the ventricular response during atrial fibrillation in some patients, however, it is our hope that clinicians will avoid the use of digitalis in the pre-excitation syndromes and reserve it only for those patients in whom elective induction of atrial fibrillation has demonstrated that the patient is not at risk for developing ventricular fibrillation. Atrial fibrillation associated with rapid conduction down an accessory pathway should be terminated immediately by cardioversion if the patient's hemodynamic measures become compromised. Under less urgent conditions, intravenous propranolol or lidocaine can be tried. For chronic management of atrial fibrillation in the pre-excitation syndrome, quinidine sulfate is the treatment of choice. Alternatively, amiodarone might be considered in countries where this is available.

In the setting of enhanced A-V node conduction, it may be equally important to evaluate the most rapid conduction achievable during atrial fibrillation despite the presence of normal QRS complexes, since a rapid ventricular response occurring across the A-V node is just as life-threatening as one sustained by an accessory pathway. While the anatomic substrate of this clinical syndrome remains controversial, it nevertheless constitutes one of the pre-excitation syndromes. Both patients with this entity reported in this study suffered ventricular fibrillation.

It is of paramount importance to determine the population of patients with pre-excitation who are at risk for developing ventricular fibrillation so that the use of digitalis may be avoided in these patients. By proper selection, it is possible to identify the population in whom digitalis can be safely used if found to be therapeutic in other respects. The method of elective atrial fibrillation allows the separation of these two groups and permits the evaluation of the effects of antiarrhythmic agents. Avoidance of digitalis in patients whose shortest R-R in atrial fibrillation is less than 300 msec would appear to afford a good margin of safety.

Addendum

Since the submission of this manuscript, we have encountered another patient in whom administration of digitalis during atrial fibrillation was followed by ventricular fibrillation. During atrial fibrillation, his shortest R-R was 250 msec, with an average R-R of 357 msec. After 1 mg of Cedilanid i.v., he developed ventricular fibrillation.

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**Cross-sectional Echocardiography in the Diagnosis of Congenital Heart Disease**

**Identification of the Relation of the Ventricles and Great Arteries**

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**SUMMARY** Using a mechanical sector-scanner, two-dimensional echocardiograms were obtained from 28 normal subjects, 15 patients with tetralogy of Fallot, 11 patients with complete transposition of the great arteries and six patients with double outlet right ventricle. The image obtained perpendicular to the long axis of the left ventricle at the base of the ventricular septum was superimposed on the image obtained perpendicular to the long axis at the origin of the great arteries. In normal subjects, these superimposed images demonstrated that the aorta originated posterior and to the left of the ventricular septum. In patients with tetralogy of Fallot, the aorta was displaced anterior and to the right resulting in the aorta overriding the ventricular septum. In patients with double outlet right ventricle both great arteries originated anterior to the ventricular septum (i.e., from the right ventricle). In patients with complete transposition, the aorta originated anterior and the pulmonary artery posterior to the ventricular septum. Thus, cross-sectional echocardiography permits noninvasive identification of the relation of the ventricles and great arteries and, therefore, provides important information for the diagnosis of patients with congenital heart disease.

**RECENT DEVELOPMENTS IN CROSS-SECTIONAL (two-dimensional) imaging of the heart with ultrasound have allowed an accurate noninvasive visualization of cardiac anatomy that has been particularly useful in evaluating patients with congenital heart disease.** Previous studies have described the application of this technique to the identification of the great arteries and the determination of ventricular situs. We used cross-sectional imaging to determine the relation of the ventricles and great arteries to each other.

**Methods**

**Patient Population**

We studied the following groups of patients: 1) 28 normal subjects (13 males and 15 females; four months to 49 years of age), 2) 15 patients with tetralogy of Fallot (nine males and six females; four to 22 years of age), 3) six patients with double outlet right ventricle (three males and three females; two to 19 years of age), 4) 11 patients with complete transposition of the great arteries (seven males and four females; two to 18 years of age).

In each of the patients with congenital heart disease, the diagnosis had been made by angiography, operation, or both, and was not known by the individual performing the cross-sectional study. Patients considered to have tetralogy of Fallot had the aorta overriding a ventricular septal defect plus infundibular pulmonic stenosis. Patients with double outlet right ventricle had normal atrial and ventricular situs, and two great arteries originating from the right ventricle. Subaortic and subpulmonic conus tissue separated both semilunar valves from the mitral valve. Of these six patients, four had either valvular or subvalvular pulmonic stenosis. In five patients the ventricular septal defect appeared to be subaortic while in the sixth it was more closely related to the pulmonic valve. Patients with complete transposition of the great arteries were those with normal atrial and ventricular situs, and D-transposition of the great arteries. Patients with a diagnosis of common or single ventricle, as well as those with dextrocardia, were excluded from this study.
Digitalis in the pre-excitation syndrome. Analysis during atrial fibrillation.
T D Sellers, Jr, T M Bashore and J J Gallagher

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