Occult arrhythmias as the etiology of unexplained syncope in children with structurally normal hearts

We evaluated six children for syncope of unknown etiology between March, 1983, and March, 1984. All had undergone previous neurologic evaluation which was normal. Cardiac examination, chest roentgenograms, and two-dimensional echocardiograms were also normal in all of the patients. Abnormal noninvasive findings in five patients included Mobitz type II atrioventricular (AV) block (one patient), sinus bradycardia (three patients), and supraventricular tachycardia (one patient). Four patients had one or more abnormal findings at invasive electrophysiologic study including evidence of sinus node dysfunction (three patients), AV node dysfunction (three patients), and distal His-Purkinje system disease (two patients). All children had a normal right heart hemodynamic catheterization. We conclude that arrhythmias are an important cause of syncope in some children with an otherwise normal heart when neurologic causes have been excluded. (Am Heart J 109:309, 1985.)

Stanley D. Beder, M.D., Mark H. Cohen, M.D., and Thomas A. Riemenschneider, M.D.
Cleveland, Ohio

Syncope is generally considered a benign symptom in children and adolescents. Vasovagal syncope is the usual diagnosis for sudden, unexpected, nontraumatic loss of consciousness in these patients. Occasional patients are found to have an atypical convulsive disorder as the basis for syncope. Traditionally, an ECG has been considered an adequate screening test to rule out cardiac arrhythmias as the etiology for syncope in a child with a structurally normal heart. In this study, we review our recent experience which suggests that occult arrhythmias are an important cause of syncope in some children with both structurally normal hearts and negative neurologic evaluations.

METHODS

Patients. Between March, 1983, and March, 1984, six patients, four boys and two girls, age 12 to 18 years with a mean age of 14.4 years, were referred to our arrhythmia service for evaluation of unexplained syncope. Patients were referred to us by pediatric cardiologists and pediatric neurologists. Each of these six patients had undergone a previous negative evaluation by a pediatric neurologist which excluded seizures, other neurologic disorders, and vasovagal reactions as possible etiologies for syncope. This work-up included a normal electroencephalogram in each patient. Because unexplained syncope is potentially life-threatening, we prospectively decided that each of these six, carefully selected children would undergo both noninvasive and invasive studies, even if the noninvasive studies were normal. Of our six patients, one patient had three episodes of syncope and the remaining five children each had a single episode of syncope. Cardiac physical examinations, chest roentgenograms, and two-dimensional echocardiograms were normal in all of the patients. Twelve lead ECGs, 24-hour Holter monitors, and maximal upright exercise tests using a modified Bruce protocol were also performed in each of the patients.

Invasive electrophysiologic testing. Following completion of the noninvasive work-up, each child underwent invasive electrophysiologic testing using standard techniques. Patients were studied in the postabsorptive state and were premedicated with meperidine, 2 mg/kg, and promethazine, 1 mg/kg intramuscularly, 30 to 45 minutes prior to the procedure. Local anesthesia was achieved with 1% lidocaine hydrochloride (<5 mg/kg). Quadripolar catheters were positioned in both the high right atrium near the sinus node and in the right ventricle at the right ventricular apex. A tripolar catheter was positioned across the tricuspid anulus to record the His bundle electrogram. A VR-16 Honeywell/Electronics for Medicine physiologic recorder was used to obtain simultaneous surface ECG.

From the Division of Pediatric Cardiology, Department of Pediatrics, Case Western Reserve University School of Medicine; and Rainbow Babies and Children's Hospital.

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Reprint requests: Stanley D. Beder, M.D., Pediatric Cardiology, Rainbow Babies and Children's Hospital, 2101 Adelbert Rd., Cleveland, OH 44106.
Figure 1. ECG from patient R.F. following implantation of a ventricular demand pacemaker for the treatment of symptomatic Mobitz type II AV block. Note the absence of PR interval prolongation prior to the nonconducted P wave. A pacemaker spike follows the blocked P wave but does not capture the ventricle (subthreshold stimulus). A junctional escape beat then occurs.

Figure 2. Surface ECG leads and endocardial recordings from patient R.F. Top to bottom: surface leads I, aV,

V, and V; endocardial leads HRA (high right atrium) and HBE (His bundle electrogram); and FAP (femoral artery pressure). A = atrial electrogram of the high right atrium near the sinus node; LSRA = low septal right atrial electrogram near the AV node; H = His bundle potential; V = ventricular electrogram. The H-V interval is abnormally prolonged to 70 msec (upper limits of normal 55 msec). The FAP is abnormal due to catheter damping.

Arrhythmias. Arrhythmias detected by noninvasive testing included sinus bradycardia (three of six patients), Mobitz type II AV block (one of six patients) (Fig. 1), and supraventricular tachycardia (one of six patients). In addition, one of the patients demonstrated an abnormal and precipitous drop in heart rate during the recovery phase of a maximal exercise test from 170 bpm at stage V to 50 bpm during the first 30 seconds of the recovery period. Five of our six patients had one or more abnormal noninvasive tests. There were a total of two of six abnormal ECGs, four of six abnormal Holter monitors, and one of six abnormal maximal exercise tests (Table I).

Numerous abnormalities were also found at electrophysiologic study (Table II). Prolonged H-V interval was measured in two of six patients (Fig. 2). Increased maximum corrected sinus node recovery time was found in three of six patients, and the total sinoatrial conduction time was increased in one of six patients. The atrial pacing cycle length causing Wenckebach or 2:1 AV conduction was abnormally prolonged in three of six patients. Prolongation of the AV node antegrade effective and/or functional refractory period was demonstrated in two of six patients. One patient had a prolonged intra-atrial conduction time and easily inducible atrial flutter. We were unable to induce ventricular tachycardia in any of the patients. Thus, abnormal electrophysiologic findings were demonstrated in four of six patients. All of the children had a normal right heart hemodynamic catheterization.

Treatment and follow-up. We implanted ventricular demand pacemakers in four of six patients (Table II). Indications for pacing included isolated sinus node dysfunction in one of four patients, combined sinus and AV node disease in two of four patients, and AV node–His-Purkinje disease in one of four patients. Digoxin alone was used in one of six
Table I. Noninvasive test results

<table>
<thead>
<tr>
<th>Patient</th>
<th>ECG</th>
<th>Holter monitor</th>
<th>Maximal upright exercise test</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.S.</td>
<td>Normal</td>
<td>Asymptomatic sinus bradycardia—lowest rate 38/min</td>
<td>Normal</td>
</tr>
<tr>
<td>R.F.</td>
<td>Mobitz II type block</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>E.P.</td>
<td>Normal</td>
<td>Asymptomatic sinus bradycardia—lowest rate 46/min</td>
<td>Stage V: heart rate 170/min; first 30 sec of recovery period: heart rate 50/min associated with fatigue and dizziness</td>
</tr>
<tr>
<td>D.W.</td>
<td>Asymptomatic sinus bradycardia—rate 46/min</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>K.S.</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>K.D.</td>
<td>Normal</td>
<td>Supraventricular tachycardia at 200/min while driving associated with dizziness</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Total abnormal tests 2/6 4/6 1/6

Table II. Results of electrophysiologic testing and treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>H-V*</th>
<th>CSNRT*</th>
<th>SACT*</th>
<th>WB CL*</th>
<th>2:1 CL*</th>
<th>AVN AERP*</th>
<th>AVN AFRP*</th>
<th>Tachycardia induction</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.S.</td>
<td>50</td>
<td>460†</td>
<td>276†</td>
<td>700†</td>
<td>550†</td>
<td>640† at SCL 930; 640† at SCL 930</td>
<td>No</td>
<td>Pacemaker</td>
<td></td>
</tr>
<tr>
<td>R.F.</td>
<td>70†</td>
<td>210</td>
<td>120</td>
<td>490†</td>
<td>400†</td>
<td>400† at SCL 710; 400† at SCL 730</td>
<td>No</td>
<td>Pacemaker</td>
<td></td>
</tr>
<tr>
<td>E.P.</td>
<td>40</td>
<td>370†</td>
<td>174</td>
<td>280</td>
<td>260</td>
<td>≤220 at SCL 710; ≤220 at SCL 730</td>
<td>No</td>
<td>Pacemaker and digoxin</td>
<td></td>
</tr>
<tr>
<td>D.W.</td>
<td>61†</td>
<td>350†</td>
<td>161</td>
<td>450†</td>
<td>§</td>
<td>315 at SCL 850; 450 at SCL 850</td>
<td>Atrial flutter†*</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>K.S.</td>
<td>43</td>
<td>184</td>
<td>216†</td>
<td>None‡</td>
<td>267</td>
<td>≤193 at SCL 683; ≤190 at SCL 500</td>
<td>317 at SCL 539</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>K.D.</td>
<td>50</td>
<td>180</td>
<td>122</td>
<td>350</td>
<td>&lt;300</td>
<td>250 at SCL 750; 260 at SCL 770</td>
<td>430 at SCL 770</td>
<td>No</td>
<td>Digoxin</td>
</tr>
</tbody>
</table>

Abbreviations: H-V = His-Purkinje conduction time (normal up to 55 msec); CSNRT = maximum corrected sinus node recovery time (normal up to 275 msec); SACT = total sinoatrial conduction time by Steenoe method (normal up to 200 msec); WB CL = atrial pacing cycle length causing AV nodal Wenckebach (normal 400 msec or less); 2:1 CL = atrial pacing cycle length causing 2:1 AV block (normal less than 400 msec and less than Wenckebach cycle length for any given patient; AVN AERP = AV node antegrade effective refractory period (normals 126-238 at cycle lengths less than 450 msec, 135-295 at cycle lengths 450-999 msec, and 148-395 at cycle lengths greater than 600 msec; AVN AFRP = AV node antegrade functional refractory period (normals 195-359 at cycle lengths less than 450 msec, 204-452 at cycle lengths 450-599 msec, and 285-501 at cycle lengths greater than 600 msec; SCL = sinus cycle length; SS, = paced cycle length; Tachycardia induction = results of attempts to induce supraventricular and/or ventricular tachycardia by programmed stimulation.

*Refer to Reference 10.
†Abnormal value.
‡Minimally abnormal value not considered as an abnormal result in the text.
§Atrial pacing cycle lengths shorter than 450 msec consistently produced atrial flutter with 2:1 to 4:1 AV block.
¶Patient went from 1:1 to 2:1 AV conduction without intervening Wenckebach cycle length; no evidence for an AV bypass tract was found.
¶¶Intra-atrial conduction time also prolonged to 55 msec (normal 10-38); atrial flutter induced easily and reproducibly by slow atrial pacing and by single atrial extrastimuli.

patients and one of six patients received no treatment. This latter patient had a normal noninvasive and invasive work-up. One of the patients with a pacemaker was also placed on digoxin for the treatment of his atrial flutter and had one further episode of syncope following pacemaker implantation. Once his pacemaker demand rate was increased from 50/min to 80/min, no further episodes of syncope occurred. None of the other patients had any recurrent syncopal episodes.

DISCUSSION

Primary conduction abnormalities. Our results indicate an unexpectedly high incidence (five of six patients) of primary conduction system disease in this carefully selected series of children with unex-
plained syncope and structurally normal hearts. We found a wide spectrum of conduction abnormalities in our patients. In fact, only one patient (E.P.) had isolated sinus node dysfunction consistent with sick sinus syndrome. Diffuse conduction system disease was found in one patient (D.W.) who had evidence of sinus, AV node, and His-Purkinje disease. Combined sinus and AV node disease was found in one patient (B.S.), while another patient (R.F.) had both AV node and His-Purkinje dysfunction.

Yabek et al. have previously reported 11 children with structurally normal hearts and sinus node dysfunction manifested as syncope and sinus bradycardia. Beder et al. have also previously reported 11 children with structurally normal hearts and sick sinus syndrome who were treated with either a ventricular demand pacemaker, antiarrhythmic medication, or both, without recurrence of syncope in any of the patients. Sinus node disease in eight children with structurally normal hearts has been reported in two separate studies by Mackintosh and by Ector and Van Der Hanwaert.

Pathologic studies by Bharati et al. have demonstrated degeneration, fibrosis, and fatty infiltration of the approaches to the sinoatrial and atrioventricular nodes in two adolescent boys, age 16 and 17 years, both of whom had had a prolonged history of documented sinus bradycardia and sinus pauses. Electrophysiologic studies had previously been performed in both patients and demonstrated extremely prolonged corrected sinus node recovery times. Bharati et al. also described the pathologic findings in the cardiac conduction systems in three adolescents who died suddenly and unexpectedly without any prior history suggesting any cardiac disease or arrhythmia. In these latter patients, all had sclerosis of the ventricular septum involving the conduction system. One of these patients also had thrombosis of the sinus node artery.

James et al. described the necropsy findings in two adolescents, 18 and 15 years of age, both of whom had died suddenly while participating in athletics. One of the patients had had a long history of recurrent dizzy spells and an irregular, slow pulse, but an ECG had never been performed. Pathologic findings in these two cases included marked narrowing and medial hyperplasia of the sinus node artery, fibrosis and degeneration of the sinus node, and degeneration of the AV node and His bundle. James et al. also described the necropsy findings in a 32-year-old man who collapsed at the wheel of his car and was pronounced dead on arrival at the emergency room. Because there was insufficient physical injury to account for death, careful examination of the heart was performed. The coronary arteries were normal. Histologic evaluation of the cardiac conduction system revealed perinodal fibrosis of the sinus node. The patient had been detected to have had asymptomatic atrial fibrillation on a routine physical examination and ECG 3 months prior to death.

Conclusions and recommendations. Unexplained syncope in children with structurally normal hearts has long been considered benign. Furthermore, the ECG has been considered an adequate screening test for the detection of arrhythmias in these patients. Although the incidence of primary conduction system disease in children is unknown, the clinical studies of Beder et al. and of Yabek et al. suggest that this problem is more prevalent than has been previously recognized. The combination of permanent pacing with or without antiarrhythmic drugs has been shown to be effective in preventing syncope in these patients. Finally, histopathologic studies of the conduction system in children who have died suddenly and unexpectedly give grim testimony to the fact that unexplained syncope in childhood is not always benign. Based on this study of carefully selected patients, we conclude that: (1) occult arrhythmias are an important cause of syncope in some children with both structurally normal hearts and negative neurologic evaluations; and (2) safe and efficacious treatment is available for these children, many of whom require pacemakers.

We therefore recommend that: (1) children who have already had negative evaluations for noncardiac causes of syncope should be thoroughly evaluated for the presence of an occult arrhythmia, even if structural heart disease is not present; (2) this evaluation should include the combination of ECG, Holter monitor, and maximal exercise testing; and (3) electrophysiologic testing should be considered in these patients.

REFERENCES

6. Bharati S, Nordenberg A, Bauertend R, Varghese JC, Car-
Comparison of acebutolol and propranolol in essential hypertension

A multicenter, double-blind study compared oral acebutolol (n = 186) with propranolol (n = 190) in the treatment of mild to moderately severe essential hypertension (diastolic ≥95 to 129 mm Hg). Both beta blockers produced significant and comparable reductions in diastolic, systolic, and mean arterial blood pressures of 16%, 12%, and 14% on acebutolol and 15%, 12%, and 14% on propranolol (all p < 0.01). At equipotent, antihypertensive doses, acebutolol induced significantly less reduction in resting heart rate than propranolol (13% on acebutolol, 17% on propranolol, p = 0.02). The mean effective doses of acebutolol and propranolol were 738 mg and 231 mg, respectively. Significantly fewer acebutolol patients experienced central nervous system side effects (acebutolol, n = 50; propranolol, n = 75; p = 0.01) or withdrew from the study prematurely due to side effects (acebutolol, n = 29; propranolol, n = 29; p < 0.01). No clinically significant trends in abnormalities of laboratory parameters were seen, and there were no statistically significant differences in the development of positive antinuclear antibody titers between the two treatment groups. It is concluded that acebutolol is as effective as propranolol in the treatment of hypertension, and acebutolol was better tolerated on the basis of heart rate and central nervous system side effects. (Am Heart J 109:313, 1985.)

Janice Wahl, M.D., Prasad Turlapaty, Ph.D., and Bramah N. Singh, M.D., D.Phil.
New York, N.Y., and Los Angeles, Calif.

Although the antihypertensive effect of beta-adrenergic-blocking agents, in general, has been well documented, considerable variation exists in efficacy and safety of these drugs, possibly because of differences in their pharmacokinetic as well as pharmacologic properties, such as cardioselectivity, intrinsic sympathomimetic activity (ISA), and/or membrane stabilizing activity. Although such associated properties may not directly affect the magnitude of blood pressure fall induced by a beta antagonist, they may nevertheless be important in permitting optimal dosage of individual agents and in the development of side effects. Acebutolol (Sectral) is a new cardioselective beta antagonist, which has weak ISA and membrane depressant properties. The latter property, however, may not be significant at clinically attainable plasma concentrations. An additional difference lies in the degree of lipid solubility; propranolol (the reference beta antagonist) is highly lipid soluble, whereas acebutolol is considerably less so. Several clinical studies have demonstrated the effectiveness of acebutolol in the management of hypertension. Propranolol, a non-selective beta blocker without ISA, was the first and is still the most widely used beta blocker in the treatment of hypertension. As there are differences...