Association of secundum atrial septal defect and atrioventricular nodal dysfunction

A genetically transmitted syndrome

BARRY J. MARON, JEFFREY S. BORER, SUN H. LAU,
ANTHONY N. DAMATO, LEWIS P. SCOTT, AND STEPHEN E. EPSTEIN

From the Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; Cardiopulmonary Laboratory, U.S. Public Health Service Hospital, Staten Island, New York; and Children's Hospital of the District of Columbia, Washington DC, USA

SUMMARY Secundum atrial septal defect may occasionally be transmitted as an autosomal dominant trait. Patients with this entity often show evidence of conduction system abnormalities by electrocardiogram. To define the nature of the conduction system disease in such patients, we studied a family in which 5 closely related members in 3 generations had the combination of atrial septal defect, syncope, and first and/or second degree atrioventricular (AV) block by electrocardiogram. Of these 5 patients, 3 had required permanent pacing. Three other relatives without syncope also had conduction abnormalities, including 1 patient with atrial septal defect. Of the 8 family members, 3 were studied with His bundle electrocardiography. Two of these 3 patients had syncope preceding operative closure of an atrial septal defect and one had no history of syncope or evidence of an atrial septal defect; all 3 had first degree AV block. Intracardiac electrophysiological study showed that each patient had a long AH time (which decreased with atropine), normal HV time, and prolonged AV nodal refractory periods. Thus, both secundum atrial septal defect and intrinsic AV nodal disease may be transmitted as autosomal dominant traits (probably as manifestations of a single mutant gene), and may occur together or separately in members of the same family.

The association of secundum atrial septal defect with prolonged atrioventricular (AV) conduction, which is transmitted as an autosomal dominant trait in certain families, represents a recognised clinical syndrome (Kahler et al., 1966; Amarasingham and Fleming, 1967; Bizarro et al., 1970; Björnstad, 1974; Emanuel et al., 1975; Pease et al., 1976). However, in all but one of these previous reports, evidence of abnormal AV conduction was obtained from the surface electrocardiogram only. Hence, the precise nature of the conduction system disease in such patients has not been defined. In the present report, we describe findings in a family in which secundum atrial septal defect was associated with a conduction disturbance localised in the AV node (as determined by His bundle electrocardiography) in several closely related relatives in 3 generations.

Selection of patients

Members of the family were originally evaluated by physical examination and electrocardiogram, as described in an earlier report (Kahler et al., 1966). The present study is concerned with recent observations made on 8 affected family members, including 2 patients not included in the earlier report. Each of these 8 patients had either a secundum atrial septal defect, electrocardiographic evidence of prolonged AV conduction, syncope, or various combinations of these findings. Each patient also had a consistently normal heart rate under basal conditions (more than 60 beats per minute in adult patients). The relevant portion of the pedigree is shown in Fig. 1. Two other members of the family (C.L. and G.L.) who were noted to have cardiac abnormalities when the family was initially screened (Kahler et al., 1966) were not available for this study. Both these patients
were second cousins to cases 4, 5, and 6. C.L. was a 27-year-old man in whom a previous electrocardiogram showed complete right bundle-branch block (QRS 0.14 s), right axis deviation, and non-specific ST segment and T wave changes. Cardiac catheterisation at age 15 years showed a normal heart without evidence of an intracardiac shunt. G.L. was a 24-year-old man who had a large atrial septal defect (Qp:Qs = 2:2) that was operatively repaired at age 11 years. Previous electrocardiograms had been normal. Neither of these men had had syncope.

Methods

HAEMODYNAMIC STUDIES
Routine right heart catheterisation was performed in the postabsorptive state using local anaesthesia but no sedation in 2 adults (cases 1 and 5), and after sedation with pethidine, chlorpromazine, and promethazine in a child (case 8), aged 2 years. None of the 3 patients was taking a cardioactive agent at the time of the study. Pressure recordings and blood samples for oxygen analysis and shunt determination were obtained in the pulmonary artery, right ventricle, right atrium, and superior and inferior vena cava. Two of the 3 patients (cases 1 and 5) were studied several years after the operative closure of atrial septal defect.

HIS BUNDLE STUDIES
After completion of the haemodynamic study, a quadripolar electrode catheter was percutaneously introduced via either an antecubital or a femoral vein and advanced under fluoroscopic guidance to the lateral wall of the right atrium near its junction with the superior vena cava. The proximal pair of electrodes was used to record a high right atrial electrogram. The distal pair of electrodes was used to stimulate the atrium. A second quadripolar catheter was percutaneously introduced via the right femoral vein and was positioned across the tricuspid valve to obtain a His bundle electrogram using methods previously described (Scherlag et al., 1969). In the 2 adult patients an additional bipolar electrode catheter was introduced percutaneously via a femoral vein and positioned in the apex of the right ventricle for the purpose of ventricular stimulation.

Intracardiac electrograms (high right atrium, low right atrium, His bundle, and right ventricle) were all recorded with filter settings at 40 and 500 Hz. Electrocardiographic leads I, II, III, and V1 (filtered at 0.1 and 200 Hz) and time lines at 10 and 100 ms were displayed on a multichannel oscilloscope and recorded on magnetic tape. The tracings were subsequently replayed and recorded on photographic paper at a speed of 150 mm per second. Refractory periods of the atrium, atroventricular node, and right ventricle were determined by the extrastimulus method (Kraer et al., 1951; Goldreyer and Bigger, 1969) during anterograde conduction using a programmed digital stimulator which delivered impulses of 1.5 ms duration at twice diastolic threshold. Each patient was paced at a constant rate to avoid the effect of changing cycle length on refractoriness. The atrium was driven at a basic cycle length and after every eighth driven beat a premature stimulus was introduced at progressively shorter intervals up to the point of atrial refractoriness. A similar procedure was used in stimulating the ventricle. Determination of retrograde AV nodal conduction time (VA) was attempted in the 2 adult patients tested, but complete retrograde VA block was present during ventricular pacing in each.

The AH interval was measured from the onset of the low atrial electrogram to the earliest onset of the His bundle deflection. The HV interval was measured from the initial His deflection to the earliest point of ventricular depolarisation on either a surface electrocardiographic lead or the intracardiac electrogram. The PA interval was measured from the onset of P wave to earliest onset of low right atrial activity. Atrial effective refractory period (A-ERP), AV node effective refractory period (AVN-ERP), and corrected sinus node recovery time (CSNRT) were measured using methods previously described (Akhtar et al., 1975; Narula, 1975). Electrophysiological measurements were made in the basal state and again after intravenous administration of atropine (0.5 mg in each adult;
Table 1  Clinical and electrocardiographic data in 8 affected members of family

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Present age</th>
<th>Sex</th>
<th>Syncope spells</th>
<th>Electrocardiograms</th>
<th>Haemodynamics</th>
<th>ASD repair</th>
<th>PR interval (s)</th>
<th>QRS interval (s)</th>
<th>Other AV conduction abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 F</td>
<td></td>
<td>At age 23 and 34 only</td>
<td>0·22</td>
<td>25/3</td>
<td>Age 37 y (secundum; 2·5 cm diameter)</td>
<td>0·09</td>
<td>Wenckebach type 2° AV block; leftward QRS axis (−20°); Rsr in V1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>68 F</td>
<td></td>
<td>Occasional</td>
<td>0·40</td>
<td>29/5</td>
<td>None</td>
<td>0·12</td>
<td>LAD (−100°)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>62 M</td>
<td></td>
<td>None</td>
<td>0·20</td>
<td>28/5</td>
<td>None</td>
<td>0·14</td>
<td>RBBB; LAD (−65°)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>22 M</td>
<td></td>
<td>Several since age 2 years; demand pacemaker inserted age 14 and no subsequent syncope</td>
<td>0·44</td>
<td>36/0</td>
<td>None</td>
<td>0·09</td>
<td>Wenckebach type 2° AV block</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>24 M</td>
<td></td>
<td>About 10 since age 10 years; demand pacemaker inserted age 20 and no subsequent syncope</td>
<td>0·28</td>
<td>18/4</td>
<td>Age 20 y (secundum; 3 cm diameter)</td>
<td>0·10</td>
<td>2° (2:1) AV block; complete heart block §</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>27 M</td>
<td></td>
<td>None</td>
<td>0·08</td>
<td>3·0</td>
<td>Age 9 y (secundum; 2 cm diameter)</td>
<td>None</td>
<td>Wenckebach type 2° AV block; Rsr in V1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6 M</td>
<td></td>
<td>One at age 6 w and one at age 5 mth; demand pacemaker inserted age 5 mth and no subsequent syncope</td>
<td>0·07</td>
<td>2·2</td>
<td>Age 4 y (secundum; 2·1) cm diameter</td>
<td>None</td>
<td>Wenckebach type 2° AV block; Rsr in V1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3 F</td>
<td></td>
<td>None</td>
<td>0·18</td>
<td>No ASD</td>
<td>28/8</td>
<td>0·05</td>
<td>Rsr in V1</td>
<td></td>
</tr>
</tbody>
</table>

* Clinically, spells were thought to be Adams-Stokes attacks, occurring during sleep and preceded by complaints of abdominal pain, nausea, malaise, and crying out; during episodes the patient would become apnoeic and cyanotic for 10 to 30 seconds with documented heart rate of 20 to 35 beats/minute.
† Clinically, spells were thought to be Adams-Stokes attacks; episodes were precipitated by straining at the toilet or noxious stimuli and consisted of brief losses of consciousness preceded by sweating, nausea, and bradycardia.
‡ During cardiac catheterisation, second degree AV block was induced by simultaneous administration of isoprenaline and Valsalva manoeuvre.
§ During cardiac catheterisation, complete heart block was induced by the administration of edrophonium (0·6 mg).
** Pulmonary arterial pressure of 30/10 mmHg with peak systolic right ventricular outflow gradient of 30 mmHg.
†† While taking digitalis.
Abbreviations: ASD, atrial septal defect; AV, atrioventricular; LAD, left axis deviation; Qp:Qs, pulmonary-to-systemic flow ratio; RV, right ventricular pressure; S/D, systolic/end-diastolic pressure.

Results

CLINICAL FINDINGS

The clinical, haemodynamic, and electrocardiographic data are summarised in Table 1 and Fig. 2. Of the 8 affected family members, 6 had haemodynamic or operative evidence of a secundum atrial septal defect. The atrial septal defect was large and required operation in 4 patients (cases 1, 5, 6, and 7); in the other 2 patients (cases 2 and 4) the atrial septal defect was small (Qp:Qs of 1·1 and 1·2, respectively, as determined by Krypton60 and dye 0·1 mg in the child), and were compared with normal values obtained in adults (Dhingra et al., 1973; Denes et al., 1974; Akhtar et al., 1975; Narula, 1975) or in children (Abella et al., 1972; Anderson et al., 1973; Levin et al., 1977).

Fig. 2  Diagram summarising salient clinical features of the eight affected members. AVB, atrioventricular block; LAH, left anterior hemiblock; RBBB, right bundle-branch block.
Table 2  Electrophysiological data in 3 patients with secundum atrial septal defect

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (y)</th>
<th>Max. Pacing CL</th>
<th>PR (ms)</th>
<th>QRS (ms)</th>
<th>PA (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Basal</td>
<td>Max. pacing</td>
<td>Atropine</td>
<td>Basal</td>
</tr>
<tr>
<td>1</td>
<td>49</td>
<td>800</td>
<td>300</td>
<td>305</td>
<td>215</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>700</td>
<td>255</td>
<td>300</td>
<td>180</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>460</td>
<td>185</td>
<td>235</td>
<td>175</td>
</tr>
<tr>
<td>Normal for cases 1 and 5</td>
<td>—</td>
<td>120-190</td>
<td>—</td>
<td>—</td>
<td>80-110</td>
</tr>
<tr>
<td>Normal for case 8</td>
<td>—</td>
<td>120-150</td>
<td>—</td>
<td>—</td>
<td>40-90</td>
</tr>
</tbody>
</table>

Abbreviations: A-ERF, atrial effective refractory period; AH, atrium to His conduction; AVN-ERF, atrioventricular node effective refractory period; CL, cycle length; CSNRT, corrected sinus node refractory time; HV, His to ventricle conduction; Max., maximum; PA, measure of intra-atrioventricular conduction (interval from onset of P wave to earliest onset of low right atrial activity as recorded on His bundle electrocardiogram).  
* data not available.

Three patients (cases 1, 2, and 3) have shown changes in their electrocardiograms over the past 10 years, with increasing leftward shift of the mean frontal plane QRS axis. In 2 (cases 2 and 3) of these patients the QRS axis ultimately exceeded −50° and in case 1 the QRS axis became −20°.

HIS BUNDLE ELECTROGRAMS
Data obtained from electrophysiological studies in the 3 patients were similar and consistent with the presence of proximal conduction system disease localised to the AV node. These data are summarised in Table 2 and shown in Fig. 3. The PR interval was prolonged under basal conditions in each patient. In addition, AH intervals and AV node effective refractory periods were prolonged in each patient under basal conditions. HV intervals were normal; block below the His bundle was not identified in any patient under basal conditions. Retrograde AV nodal conduction (VA) was not seen during ventricular stimulation. However, the exact location of retrograde AV nodal block was not identified since retrograde His potentials were not observed during AV dissociation. Split His potentials were not observed, thereby excluding the possibility of intra-Hisian block. In one patient (case 5) His bundle pacing resulted in 1:1 ventricular activation up to 200 beats per minute, with QRS complex morphology identical to that seen during sinus rhythm. In addition, atrial pacing resulted in AV nodal block at heart rates slower than 200 beats per minute, indicating that the conduction abnormality in this patient was in the AV node and not in the His-Purkinje system.

In each patient, with the administration of atropine, PR intervals decreased, AH intervals and AV node effective refractory periods shortened (but not to normal for subjects who had not received atropine), and HV intervals were unchanged. With dilution curve analyses) and no operation was performed.

Cases 4, 5, and 7 with atrial septal defect experienced repeated episodes of syncope for which permanent demand right ventricular pacemakers had been inserted. None of these 3 patients has had a syncope episode since insertion of the pacemaker (3, 5, and 7 years later, respectively). Two other patients with atrial septal defect have had syncope attacks, but have not had pacemakers inserted; 1 (case 1) of these 2 patients had a history of 2 syncope attacks, but none within the past 15 years, while the other patient (case 2) continues to have occasional episodes of syncope at age 68 years without serious consequences. One patient (case 6), who had a large atrial septal defect closed at operation, has remained asymptomatic.

Both of the patients without an atrial septal defect (cases 3 and 8) are asymptomatic. Each, however, has a conduction abnormality on surface electrocardiogram (first degree AV block in case 8 and bifascicular block in case 3).

ELECTROCARDIOGRAPHIC FINDINGS
Of the 8 patients, 7 showed consistent prolongation of the PR interval on the surface electrocardiogram. PR intervals ranged from 0·18 s in case 8, a 2-year-old infant (upper limit of normal 0·15 s), to 0·44 s. The remaining patient (case 3) had a borderline PR interval of 0·20 s. QRS duration was normal in 6 patients and prolonged (≥ 0·12 s) in cases 2 and 3.

The precise mechanism of syncope in the 5 patients had not been defined by electrophysiology. In particular, complete heart block was not documented in these patients, except transiently in case 5 after administration of edrophonium. However, 2 of the patients (cases 1 and 4) with syncope had several documented periods of Wenckebach type second degree AV block; case 7 showed this conduction abnormality only while taking digitals.
rapid atrial pacing, PR and AH intervals increased and HV interval did not change.

QRS duration was normal under basal conditions in each patient, and did not change during rapid atrial pacing, with extrastimuli during pacing, or with the administration of atropine. There was no other alteration in intraventricular conduction under these conditions, either on the surface electrocardiogram or on the His bundle electrogram which showed no anterograde infra-Hisian block. These findings suggest that, in the patients studied, functionally important disease of the distal conduction system was absent. Of interest, the corrected sinus node recovery time (Krayer et al., 1951) was prolonged in both adult patients, suggesting the presence of sinus node dysfunction. However, PA times were normal indicating that there was no abnormality of intra-atrial conduction. In each of the 3 patients studied, right heart haemodynamics were normal and there was no evidence of an intracardiac shunt.

### Discussion

The data in this report indicate that secundum atrial septal defect and intrinsic AV nodal disease may occur together or separately in members of the same family. The family we studied includes 5 closely related members in 3 generations with secundum atrial septal defect and syncope, as well as either first degree AV block, second degree AV block, or both, on electrocardiogram. It is, therefore, likely that in this particular family an autosomal dominant pattern of transmission for this syndrome exists.

Secundum atrial septal defect appears to have an increased prevalence in certain families (Carleton et al., 1958; Zetterqvist, 1960; Campbell and Polani, 1961; Howitt, 1961; Weil and Allenstein, 1961; Zuckerman et al., 1962; Johansson and Sievers, 1967; Nora et al., 1967; Nora, 1968; Zetterqvist et al., 1971; Libshitz and Barth, 1974; Nora and Nora, 1976). In these few families the genetic transmission appears to be most consistent with either an autosomal
dominant (Zetterqvist, 1960; Campbell and Polani, 1961; Howitt, 1961; Zuckerman et al., 1962; Johansson and Sievers, 1967; Zetterqvist et al., 1971; Libshitz and Barth, 1974) or autosomal recessive (Carleton et al., 1958; Campbell and Polani, 1961; Nora et al., 1967) trait. However, Nora et al. (1967) have emphasised that multifactorial inheritance seems to account for the majority of cases of atrial septal defect. Nevertheless, in those particular families in which the pattern of inheritance seems most consistent with autosomal dominant transmission, secundum atrial septal defect may often coexist with AV conduction abnormalities, as seen on the surface electrocardiogram (Kahler et al., 1966; Amarasingham and Fleming, 1967; Bizarro et al., 1970; Björnstad, 1974; Emanuel et al., 1975; Pease et al., 1976). In these families the electrocardiographic conduction abnormality is most commonly first degree AV block, though second degree AV block of the Wenckebach type and complete heart block also occur.

Data obtained from our His bundle electrocardiograms provide evidence that the conduction system abnormality in the patients studied is localised primarily in the AV node. Cases 1 and 5 each of whom had atrial septal defect, first and/or second degree AV block, and syncope (case 5 required a permanent pacemaker) showed prolonged AH time and normal HV time. These findings are similar to those briefly described in a patient with secundum atrial septal defect, first degree AV block, and intermittent second degree AV block of the Wenckebach type (Pease et al., 1976).

It is worth emphasising that the shortening of AH times and AV nodal refractory periods which followed the administration of atropine to our 3 patients who had electrophysiological studies showed only that vagal tone was present. Increased vagal tone, however, cannot be incriminated as the sole cause of the electrocardiographic and electrophysiological findings in our patients because each of the 8 patients studied showed consistently normal heart rates under basal conditions.

The finding on the electrocardiogram of left axis deviation and prolonged QRS duration in cases 2 and 3, and leftward progression of the QRS axis in case 1 suggest that the conduction disease is not localised entirely to the AV node in these patients. Nevertheless, all 3 patients studied with His bundle electrocardiograms (including case 1) showed normal HV time. Moreover, neither rapid atrial pacing, extrastimuli, nor atropine resulted in deterioration in distal conduction (QRS complexes and HV time were unchanged) or block below the His bundle. Hence, it appears that, in these patients, functionally important disease of the distal conduction system is not a part of this syndrome, at least at this time.

The mechanism of syncope in patients with atrial septal defect and intrinsic AV nodal disease is unclear. However, it is possible that such syncope is explained by potentiation of conduction delays resulting from transient increases in vagal tone. However, in previous descriptions of this syndrome syncope has been an uncommon manifestation.

Of interest, case 8 (daughter of case 5), who had first degree AV block but no atrial septal defect, showed abnormalities on the His bundle electrograms similar to those seen in cases 1 and 5. These findings suggest that the AV nodal disease present in this syndrome may be genetically transmitted independently of, as well as in association with, an atrial septal defect. However, we cannot exclude the possibility that incomplete genetic penetrance is responsible for this variable phenotypic expression of the syndrome. While it cannot be established from our study whether the AV nodal disease and atrial septal defect were transmitted on one or two gene loci, it seems most likely that a single locus is responsible and that these two abnormalities are therefore manifestations of a single mutant gene.

Although AV nodal disease was the predominant abnormality in our patients, both adult patients also had slightly prolonged sinus node recovery times, suggestive of a sinus node abnormality. Hence, we cannot exclude the possibility that syncope in our patients was the result, in part, of sinus node dysfunction. Furthermore, these observations suggest a close relation between sinoatrial and AV nodal development, and may be relevant to the reported presence of AV nodal disease in some patients with sick sinus syndrome (Narula, 1971).

References


ASD and AV nodal dysfunction


Requests for reprints to Dr Barry J. Maron, Cardiology Branch, National Heart, Lung, and Blood Institute, Building 10, Room 7B-15, Bethesda, Maryland 20014, USA.