Atrioventricular Node Fetal Dispersion and His Bundle Fragmentation of the Cardiac Conduction System in Sudden Cardiac Death

M. PAZ SUAREZ-MIER, MD, Ph.D*, CARLOS GAMALLO, MD, Ph.D†
Madrid, Spain

Objectives. This study sought to examine the frequency of persistent fetal dispersion of the atrioventricular (AV) node and fragmentation of the atrioventricular bundle (His) bundle in the cardiac conduction system of sudden cardiac death cases and control subjects to establish their importance as the cause of death.

Background. These are two of the most frequent lesions reported in published reports in the cardiac conduction system in unexplained sudden deaths.

Methods. We have studied the conduction system of 347 hearts: 249 hearts from sudden cardiac death cases and 98 control hearts. The sudden cardiac death cases were divided, according to the pathology found, in three groups: group I: ischemic heart disease, 137 cases; group II: nonischemic heart disease, 48 cases, and group III: unexplained sudden cardiac deaths, 64 cases. The control group (group IV) consisted of patients with unnatural deaths and extracardiac natural deaths.

Results. Persistent fetal dispersion of the AV node was observed in 70 cases (20.17%) of all groups with a frequency (40.81%) statistically higher in the control group. Fragmentation of the His bundle was observed in 95 cases (31.77%), and the frequency was statistically higher in the control group, too (47.67%).

Conclusions. Persistent fetal dispersion of the AV node and fragmentation of the His bundle can be a normal variation present during many years in life and must not be considered the anatomic substrate for arrhythmias and sudden death without electrocardiographic abnormalities.

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Ischemic heart disease is the most frequent cause of sudden death in adults (1,2), whereas hypertrophic cardiomyopathy, myocarditis, anomalous origin of coronary arteries, aortic stenosis, Fallot tetralogy, pulmonary hypertension and others are more frequent in children and teenagers (3–6). However, in many cases of sudden death in the young (5% to 42%), the hearts are structurally normal and no cause of death is found (3,4,7–11). Many pathologist, including us, have focused on the cardiac conduction system (CCS) to find structural abnormalities in cases of unexplained sudden death (5,12–23). Two of the most frequent abnormalities reported in these studies are the persistent atrioventricular (AV) node fetal dispersion described by James et al. (21,22,24–26) and the fragmentation of the atrioventricular bundle (His) bundle described by Bharati et al. (14–16,18–20).

The necessity of an appropriate control group to value the conduction system anomalies has been reported (27,28). In this work we report the incidence of these two abnormalities in the conduction system of sudden cardiac death cases and controls to establish their relevance.

From the *Section of Histopathology, Institute of Toxicology and †Department of Pathology, La Paz Hospital, Madrid, Spain. This work was supported in part by the Institute of Toxicology of Madrid and in part by the Spanish Cardiology Society.

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Address for correspondence: Dra. M. Paz Suárez-Mier, Instituto de Toxicología, Luis Cabrera 9, 28002 Madrid, Spain. E-mail: histop@mad.inaltox.es.

Methods

The CCS of 347 hearts were studied; 249 were hearts from sudden cardiac death cases and 98 normal hearts were used as control hearts. In the sudden cardiac death cases a complete forensic autopsy was performed with no meaningful extracardiac abnormality and negative toxicologic analysis.

The sudden cardiac death cases were divided, according to the pathology found, in three groups:

Group I: Sudden cardiac death cases with ischemic heart disease. We considered in this group those cases with severe atheromatous coronary lesion (cross-sectional area reduced >75%, in at least one of the major epicardial coronary arteries [1,2]; coronary thrombosis; acute or old myocardial infarction) or nonatherosclerotic coronary disease.

Group II: Sudden cardiac death cases with nonischemic heart disease.

Group III: Sudden unexplained deaths without meaningful lesions (mild myocardial hypertrophy, mild atheromatous coronary lesion or nothing at all).

The last group (group IV) includes 98 control cases: 80 men and 18 women (mean age 39.41 ± 19.97). The causes of death in this group were: traumatic death cases (37), sudden death related to drug abuse (25), asphyxial deaths (9), toxic deaths...
(12), gun shot deaths (2), electric fatalities (2) and extracardial natural sudden deaths (11).

**Method for examination of the CCS.** The conduction tissue was studied as follows. A block of the right atrium including the sulcus terminalis was obtained to study the sinoatrial node. From this block four to five sections were obtained. Another block was excised from the anterior margin of the coronary sinus to the medial papillary muscle of the right ventricle, including 1 cm of atrium and ventricle on either side of the tricuspid ring valve. The block removed was cut along planes perpendicular to the annulus, from posterior to anterior, obtaining five to seven blocks, 2 mm in width. These blocks were automatically processed and embedded in paraffin. From each block at least two sections were obtained. In those cases with suspicious lesions the paraffin block was cut serially. The sections were stained with hematoxylin–eosin and Masson trichrome.

Persistent fetal dispersion is defined as islands of conduction tissue separated from the AV node and dispersed in the central fibrous body (26,29) (Fig 1a). The septation of the His bundle is characterized by fragmentation of the main bundle, which form loops in some cases (18) (Fig. 1b).

**Statistical analysis.** Statistical analysis was performed with the BMDP program (PC 90 version). The analysis of variance test was used for the age of the groups and Pearson chi-square test for the frequency of the lesions.

**Results**

**Cardiac death pathology.** Ischemic heart disease, as defined previously (group I), was observed in 137 cases: 115 men

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**Abbreviations and Acronyms**

- **AV** = atrioventricular
- **CCS** = cardiac conduction system

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![Figure 1](image-url)  
(a) Islands and tongues of conduction tissue (arrowheads) separated from the atrioventricular node (AV node), embedded in the central fibrous body. Masson trichrome O.M. ×4, reduced by 70%.  
(b) Fragmentation or septation of the His bundle. Masson trichrome O.M. ×4, reduced by 70%.
Table 1. Number, Gender and Mean Age of the Four Groups

<table>
<thead>
<tr>
<th>Group I, IHD</th>
<th>Group II, NonIHD</th>
<th>Group III, USD</th>
<th>Group IV, Control</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>137</td>
<td>48</td>
<td>64</td>
<td>98</td>
</tr>
<tr>
<td>M/F</td>
<td>115/22</td>
<td>36/12</td>
<td>45/19</td>
<td>80/18</td>
</tr>
<tr>
<td>Mean age (years)*</td>
<td>54.7 ± 15.45</td>
<td>48.29 ± 22.16</td>
<td>40.37 ± 21.86</td>
<td>39.41 ± 19.17</td>
</tr>
</tbody>
</table>

*Analysis of variance test p = 0.0001. IHD = ischemic heart disease; NonIHD = nonischemic heart disease; USD = unexplained sudden death.

and 22 women (mean age 54.7 ± 15.45 years) (Table 1). The coronary lesions were severe atheromatous coronary disease in 98 cases (71.53%), occlusive thrombosis in 37 cases (27%) and coronary dissecting hematomas in 3 cases (2.18%). The myocardial lesions were old ischemic lesions in 64 cases (46.71%) and acute myocardial infarction in 31 cases (22.62%), and there were no significant myocardial lesions in 42 cases (30.65%).

Nonischemic heart disease (group II) was observed in 48 cases: 36 men and 12 women (mean age 48.29 ± 22.16 years) (Table 1). The heart disease in this group included: severe myocardial hypertrophy (heart weight >500 g): 23 cases; aortic stenosis: 5 cases (three bicuspid valves, one senile and one supravalvular); rheumatic mitral valve disease: 3 cases; infective aortic valve endocarditis: 1 case; dilated cardiomyopathy: 4 cases; arrhythmogenic cardiomyopathy: 4 cases; myocarditis: 3 cases; pulmonary hypertension: 2 cases; pulmonary thromboembolism: 2 cases; and aortic dissection: 1 case.

No meaningful structural heart disease (unexplained deaths) was observed in 64 sudden cardiac death cases (group III): 45 men and 19 women (mean age 40.37 ± 21.86 years) (Table 1).

Concerning the mean age of the groups, statistically significant differences (p < 0.0001) were observed between all of them (Table 1) and between groups I and III (p < 0.0001); between groups I and IV (p < 0.0001), and between groups II and IV (p = 0.0196).

Conduction system findings. Persistent fetal dispersion of the AV node was observed in 70 cases (20.17%) with a mean age of 41.51 ± 16.43 years (Table 2). The statistical analysis showed significant differences comparing the four groups and comparing the three sudden cardiac death groups altogether with control subjects (p < 0.05), whereas no difference was observed among the sudden cardiac death groups (p > 0.05) (Table 4). No statistical difference was observed with respect to the mean age in the groups.

The penetrating His bundle was studied in 299 cases distributed in the four groups as is seen in Table 3. Fragmentation or septation of the His bundle was observed in 95 cases (31.77%) with a mean age of 42.3 ± 19.04 years (Table 3). Statistically significant differences (p < 0.05) were observed also comparing the four groups and sudden cardiac death groups with control subjects (Table 4). Concerning the mean age no difference was observed among the groups.

Discussion

Technique for the examination of the CCS. Although some authors consider necessary the examination of the CCS as a routine procedure during postmortem studies, especially in sudden cardiac death cases (19,22), the time-consuming methods performed by specialized laboratories, where hundreds or thousands of sections are examined per case (19,29–39), are unfeasible for nonspecialized laboratories, such as forensic ones, where hundreds of autopsies are studied each year. The simplified method used in this work has been previously described in sudden cardiac death series (40,41) and it is able to identify the major structures of the conduction system: sinoatrial node, AV node, His bundle and proximal bundle branches, if the serial blocks are slender enough. Thanks to this method it is possible to study the CCS of a large number of hearts as in our series. However, if the penetrating His bundle is short, it can be missed (48 out of 347 hearts of our series). In our experience (first author’s PhD thesis) most of the lesions described in the CCS in sudden cardiac death cases can be found by this simplified method. Obviously some anomalies such as accessory pathways can only be demonstrated by serial examination.

CCS development. During the normal development of the atrioventricular conduction system bridges of conduction tissue extend through the sulcus tissue to connect the nodal bundle axis with the ventricular musculature. As intrauterine development continues, the sulcus tissue matures in the region of the membranous septum and, as the collagenous tissue

Table 2. Persistent Fetal Dispersion of the AV Node

<table>
<thead>
<tr>
<th>Group I, IHD (n = 137)</th>
<th>Group II, NonIHD (n = 48)</th>
<th>Group III, USD (n = 64)</th>
<th>Group IV, Control (n = 98)</th>
<th>Total (n = 347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>14</td>
<td>7</td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>%</td>
<td>(10.21%)</td>
<td>(14.58%)</td>
<td>(14.06%)</td>
<td>(40.81%)</td>
</tr>
<tr>
<td>Mean age</td>
<td>50.50 ± 14.76</td>
<td>43 ± 22</td>
<td>37.44 ± 14.16</td>
<td>39.02 ± 15.81</td>
</tr>
</tbody>
</table>

*Chi-square p < 0.0001. AV = atrioventricular; IHD = ischemic heart disease; NonIHD = nonischemic heart disease; USD = unexplained sudden death.
develops, the nodoventricular and fasciculoventricular extensions become dispersed within the central fibrous body as the “archipelagos” (42). Later, the AV node and His bundle undergo remarkable morphologic transformation beginning about 1 or 2 weeks after birth that must be finished during the first year of life. James pointed out two possible mechanisms responsible for the process: resorptive degeneration produced by pluripotential fibroblasts present in the central fibrous body that smooth the irregular borders (archipelagos) of the fetal AV node and His bundle (21,26,43,44) or a mechanism of apoptosis responsible for pruning away this surplus tissue (45,46).

**Functional significance.** According to James et al. (21,22,26,45) cell death or resorptive degeneration of the AV node or His bundle can produce transient periods of electrical instability, as loop short circuits of nodal tissue distributed in the central fibrous body constitute potential routes of abnormal reentry and the pockets of nodal tissue in the central fibrous body could serve as eccentric sites of abnormal automaticity. A delay or absence of this resorption results in an increased chance for arrhythmias and sudden death (24–26). In a series of 18 victims of Pokkuri disease (sudden, unexplained, nocturnal death involving apparently healthy young men among ethnic groups of Asian descent) Kirschner et al. (27) observed fetal dispersion of the AV node in 14 hearts associated with similar dispersion of the His bundle in 12 hearts. In 11 cases with fetal dispersion one or more accessory pathways were described.

On the other hand, Bharati and Lev (14–16,18–20) have reported many cases of sudden death in which there was, together with many others abnormalities of the CCS, fragmentation or looping of the His bundle. The consequences of this alteration should be intrahisian slowing of the conduction producing reentrants, increased automaticity, paroxysmal block (due to fractionation of the impulse transmission through the abnormal structures), ventricular arrhythmias and sudden death (15,16,47).

Persistent fetal dispersion of AV node and His bundle fragmentation may be silent throughout life but an altered physiologic state such as changes in local vascular tone (coronary spasm), great emotional stress, increased vagal activity, fever and mild acidosis can trigger sudden death (12,19–21,25,26,45).

**Interpretation of our results.** In our series we have observed these two abnormalities very frequently and in advanced adulthood (Tables 2 and 3). We think the explanation for this discrepancy in comparison with the reports of James et al. and Bharati et al. need not lie in the number of sections examined from each case; since we have found these lesions so frequently examining few slides, probably the frequency should be higher if we had studied it serially. That discrepancy could be explained by the control cases in their series. James dissected and examined histologically over 1000 human hearts, but primarily from cases of sudden unexpected death (48). In a review of his work we found that in 1961 James studied the human atrioventricular node of 81 hearts (“normal and abnormal”) between 18 and 82 years including three infants (49). In 1976 he and Massing studied only 32 human hearts from live birth to 87 years old from noncardiac cause of death and from cardiac disease without electrocardiographic abnormalities (38). On the other hand, in Bharati and Lev reports (16,17,50) the control cases for the AV node and His bundle are from a report published by Erickson and Lev in 1952. In that report they studied the conduction system of 68 hearts from 5.5 months gestation age to 81 years old, but they do not explain the cause of death (51).

Regarding this issue, Rossi and Matturri (28) have pointed out: “a further shortcoming in the treatment of this subject (sudden cardiac death) depends on the extreme paucity of reliable contributions from the literature, due to lack, or inaccuracy, of post-mortem controls on the conduction and nervous system in victims of sudden cardiac death.” In a recent analysis of the CCS of 100 cases under 30 years of age from traumatic and noncardiac sudden death cases performed by

### Table 3. His Bundle Fragmentation

<table>
<thead>
<tr>
<th></th>
<th>Group I, IHD (n = 106)</th>
<th>Group II, NonIHD (n = 46)</th>
<th>Group III, USD (n = 61)</th>
<th>Group IV, Control (n = 86)</th>
<th>Total (n = 299)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>22</td>
<td>17</td>
<td>15</td>
<td>41</td>
<td>95*</td>
</tr>
<tr>
<td><strong>%</strong></td>
<td>(20.75%)</td>
<td>(36.95%)</td>
<td>(24.59%)</td>
<td>(47.67%)</td>
<td>(31.77%)</td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>50.18 ± 13.33</td>
<td>44.11 ± 23.09</td>
<td>39.06 ± 21.06</td>
<td>38.61 ± 18.35</td>
<td>42.34 ± 19.04</td>
</tr>
</tbody>
</table>

*Chi-square p = 0.0004. IHD = ischemic heart disease; NonIHD = nonischemic heart disease; USD = unexplained sudden death.

### Table 4. Statistical Analysis

<table>
<thead>
<tr>
<th></th>
<th>Persistent Fetal Dispersion</th>
<th>His Bundle Fragmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD</td>
<td>30</td>
<td>54</td>
</tr>
<tr>
<td>Control</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>95</td>
</tr>
<tr>
<td>Chi-square</td>
<td>p &lt; 0.0001</td>
<td>p = 0.0002</td>
</tr>
<tr>
<td>IHD</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>NonIHD</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>USD</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>54</td>
</tr>
<tr>
<td>Chi-square</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
</tr>
</tbody>
</table>

SCD = sudden cardiac death; IHD = ischemic heart disease; NonIHD = nonischemic heart disease; USD = unexplained sudden death.
Cohle and Lie, they observed persistence of fetal dispersion in 90 cases (29). The incidence was higher than ours, probably because they have studied a younger population.

As these lesions are characteristic of the development of the conduction system, it was predictable that the frequency in the ischemic group (group I) and nonischemic heart disease group (group II) would be smallest because the mean age in these two groups was higher than in the sudden unexplained death and the control groups (Table 1). But the low frequency of these lesions in group III in comparison with the control group was surprising, as the mean age was similar in both (Table 1). We could speculate that perhaps in some cases of sudden death in young people an accelerated morphogenesis is implicated in death, in a way similar to some AV blocks detected very early after birth (22) or in some familial arrhythmias where excessive segmentary resorption of the His bundle has been reported (52).

Limitations. Only serial examination of the cardiac conduction tissue can demonstrate accessory pathways, and it is possible that in some of our sudden unexplained death cases tongues of tissue from the persistent fetal dispersion or His bundle fragmentation connect with the ventricular septum (Mahaim fibers). In those cases the association of the two lesions could explain sudden death.

Conclusions. We think, as Davies et al. postulated previously (42), that fetal dispersion and/or His fragmentation can be a normal variation present during many years in life and must not be considered the anatomic substrate for arrhythmias and sudden death without electrocardiographic abnormalities.

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References


