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Cardiac Atrioventricular Junctional Tissues in Hearts From Infants Who Died Suddenly

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The cause of sudden infant death syndrome is not known at present. Most agree that in the majority of cases it involves primary apnea. However, cardiac abnormalities probably account for a subset of these deaths. An investigation into the structure of the atrioventricular (AV) junctional tissues of the heart would provide insight into the frequency of sudden death in infants that might result from abnormal cardiac morphology. The hearts of seven infants who died from diagnosed sudden infant death syndrome were examined by serially sectioning and studying this critical region of the heart.

The hearts of these infants could be divided into three groups on the basis of their morphologic features. In the first group, represented by two cases, there were marked variations from normal, the most striking feature being the presence of accessory pathways. In the second group, represented by four cases, the AV junctional tissues were not fully mature and clusters of AV nodal and bundle cells were dispersed throughout the anulus fibrosus. In the third group, the structure of the junctional tissues was normal. There remains a distinct subset of infants who might have died suddenly and unexpectedly from cardiac abnormalities that needs to be more completely defined.

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Death of sudden unknown causes occurs in infants at the rate of 2 per 1,000 in the general population (1). The death of these apparently normal children often occurs between the second week of life and 2 years of age (2), although the most common age range is between 1 week and 10 months (median 3 months) (3). There have been multiple causes proposed for the sudden infant death syndrome and these have been extensively reviewed in recent years (4–7).

There is convincing evidence that the major cause of sudden infant death is primary apnea rather than problems with the heart (7). This conclusion is made, at least in part, on the basis of an examination of 400 near-miss cases. Near-miss infants are those infants who have been successfully resuscitated after having episodes of apnea and cyanosis with bradycardia (7). Arrhythmias were not found to be the probable or at least frequent causes of the near-miss episode in these cases. The cause of the primary apneic episode is not currently known, however.

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Reports have been made of abnormalities in the cardiac conduction system when it has been examined morphologically in some infants who died suddenly (8–13). These findings have been disputed by some investigators (5,7,14–16), although cases such as those presented by Sturner et al. (13) do provide strong evidence that in a subset of these infants death is due to lethal cardiac arrhythmias. It must be stated clearly, however, that postmortem studies on infants who die suddenly and unexpectedly can do no more than provide anatomic substrates for lethal cardiac arrhythmias and do not prove that such arrhythmias ever existed.

Some studies (13,15) have demonstrated that accessory pathways are present in some infants who die suddenly. Accessory pathways have also been implicated in Wolff-Parkinson-White syndrome, which can cause lethal cardiac arrhythmias (7). Our hypothesis is that although the majority of deaths from the sudden infant death syndrome are from primary apnea, abnormalities in the cardiac conduction system probably account for a small proportion of these deaths. Although we cannot directly test this hypothesis, we have begun to study infants who died suddenly and unexpectedly in the hope that we can begin to determine the frequency of morphologic abnormalities in the cardiac conduction system. These data could then be considered the upper limit in the possible incidence of sudden infant deaths caused by cardiac conduction system abnormalities.

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Methods

Study cases. Hearts from seven infants who died of the sudden infant death syndrome underwent routine postmortem study. They were examined at the gross anatomic level and then cut into five blocks. One was the right anterior lateral atrioventricular (AV) junction, which included the atrial and ventricular attachments into the lateral portion of the anulus fibrosus. The second block was the right posterior lateral AV junction and it included the base of the atrial and top of the ventricular musculature. The same procedure was used on the left side of the heart, and this yielded two more blocks: the left anterolateral and the left posterolateral AV junction. The final block taken was the septal block, which included the top of the interventricular septum and the base of the interatrial septum. This last block contained the tissue from the pulmonary outflow tract to that region of the AV junction posterior (inferior) to the coronary sinus (17).

Histologic preparation. The hearts had been fixed in formalin, and after they had been cut into the five blocks, each was washed overnight in water, dehydrated, cleared and embedded in paraffin. The blocks were embedded so that the plane of section was in the frontal plane of the heart. Ten μm serial sections were cut and every section was placed on slides and saved for future examination. Initially, every tenth slide was stained with hematoxylin-phloxine-saffranin stain. This made it possible in the initial study to identify the general location of the cardiac conduction system and also the possible regions where accessory pathways might exist. In critical regions, every other slide was stained with the hematoxylin-phloxine-saffranin stain for subsequent study. In some areas, every slide was stained to insure a complete examination of the specialized conducting tissues of the heart.

Case Reports

Case 1. A 4 month old white male infant died suddenly at home of unexplained causes. The infant died in August and was discovered dead in bed at 9:00 AM. Autopsy revealed slight biventricular hypertrophy of the heart with a small, clinically regressing, membranous septal defect. Otherwise, the autopsy revealed no other abnormalities. The stated diagnosis was sudden infant death syndrome.

Histology. The left and right lateral AV junctions were normal in this infant. The anulus fibrosus was well developed and separated the atrial myocardium from the ventricular myocardium. There was no evidence of accessory pathways in the lateral junctions. The distal AV bundle was morphologically normal, the right and left bundle branches arising in the expected anatomic position. The bundle penetrated a well formed anulus fibrosus (Fig. 1a) and joined the AV node. In addition to this normal AV connection, there was an accessory pathway located further posterior to the point at which the AV bundle penetrated the anulus (Fig. 1b). The subendocardial atrial myocardium, which bypassed the AV node, passed through the anulus fibrosus and connected to the ventricular myocardium of the interventricular septum. In other respects, this heart was normal with a morphologically normal AV node and surrounding transitional zone. Therefore, in addition to the structurally normal AV junctional tissues, there was another pathway that linked the atrial to the ventricular myocardium.

Case 2. This 3 month old black male infant died suddenly in bed in June. He was put to bed at 10:00 PM and was found dead at 10:00 the next morning. The child was in good health up to 2 days before death, when he was found to have symptoms of an upper respiratory infection with a cough. The family history is significant in that the father has had six sons who have all died in infancy. His daughters are all alive and well. Despite signs of an upper respiratory infection, which included congestion of the lungs and tracheobronchial tree, this infant was diagnosed as having died of sudden infant death syndrome.

Histology. The lateral AV junctions in this heart were structurally normal. In all sites examined, no connection between the atrial myocardium and the ventricular myocardium existed. The anulus fibrosus in these lateral regions

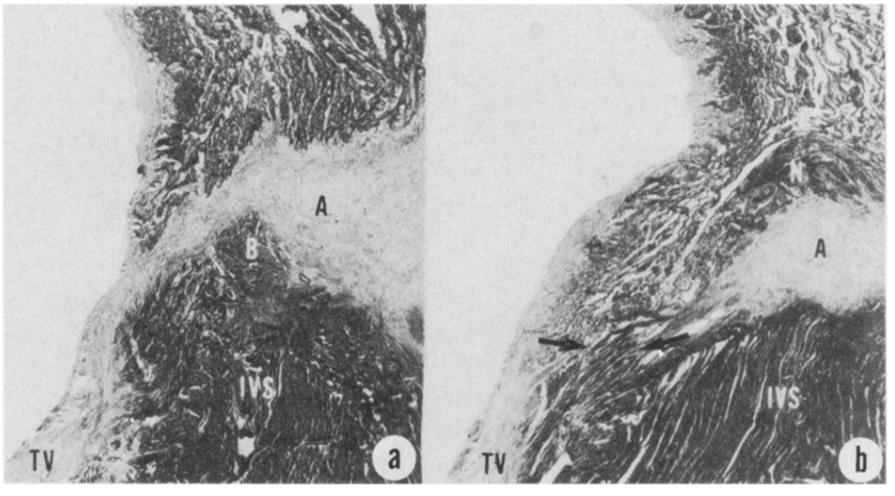

Figure 1. Case 1. Two light microscopic sections from the heart. **a**, The nonpenetrating nonbranching segment of the atrioventricular bundle (B) is located below the well developed anulus fibrosus (A). **b**, A large defect in the anulus is seen between the two **arrows** with an accessory pathway that bypasses the atrioventricular node (N) passing through the defect. IAS = interatrial septum; IVS = interventricular septum; TV = tricuspid valve. (Magnification ×20, reduced by 30%.)

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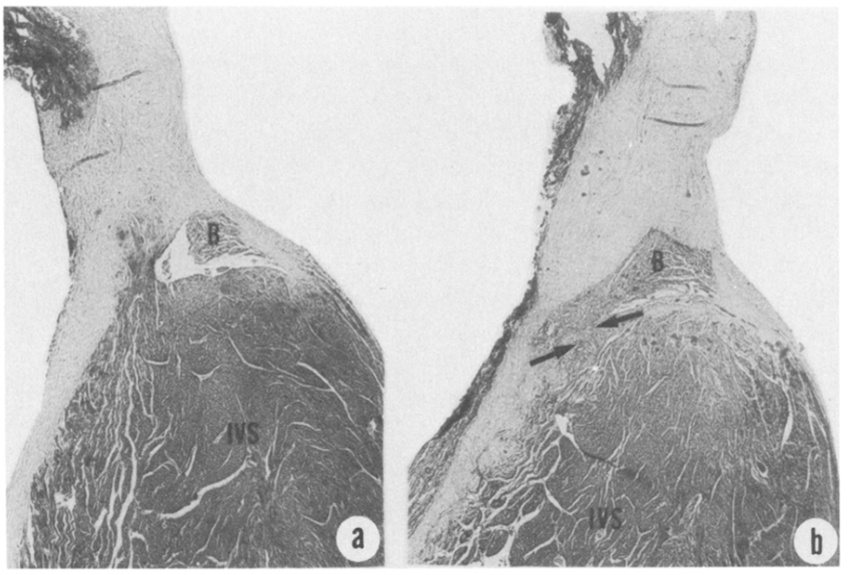

Figure 2. Case 2. Two light microscopic sections from the heart. **a**, The nonpenetrating nonbranching portion of the atrioventricular bundle (B) is located on the left side of the interventricular septum (IVS). **b**, Further posteriorly, the atrioventricular bundle (B) remains on the left side of the septum. There is also a fasciculoventricular connection seen between the **arrows** connecting the bundle cells to the interventricular septal musculature. (Magnification ×20, reduced by 30%.)

was morphologically normal. A distinct origin of the right bundle branch was not apparent when the AV bundle was examined. As the bundle continued proximally toward the AV node, it remained on the left side of the interventricular septum and the subsequent region of the septum between the left ventricle and the right atrium. The left-sided bundle (Fig. 2) displayed connections with the interventricular septal musculature. There was dispersion of the AV nodal tissue, including a separation of the two segments of the node into left and right segments, as well as disruption of the transitional cells from the perinodal region.

Case 3. This 14 month old black male child was found dead in bed in the morning. He died in August. He was born prematurely, but had been well during his first year of life. The diagnosed cause of death was sudden infant death syndrome.

Histology. The lateral AV junctions were morphologically normal. The atrial musculature was clearly separated from the ventricular myocardium by a well formed anulus fibrosus. Examination of the AV junctional tissues showed that there were four major morphologic alterations: 1) fibrosis was present around the proximal portion of the AV bundle where the left bundle branch was originating (Fig. 3a); 2) there was an ischemic portion of the nonbranching, nonpenetrating portion of the AV bundle; 3) there was an increase in the size of the anulus that had two ramifications: a) displacement of the AV node and bundle to the right side of the septum (Fig. 3b), and b) clusters of AV nodal and bundle cells were located in the connective tissue that constituted the anulus (Fig. 3b); 4) there were left- and right-sided atrial bypass tracts that bypassed the node and bundle and directly connected the atrial musculature to the bundle of His. The transitional cells were normal as they connected the atrial musculature to the AV nodal cells.

Case 4. This black female infant was 6 months old when she was found dead in bed one morning in December. Sev-

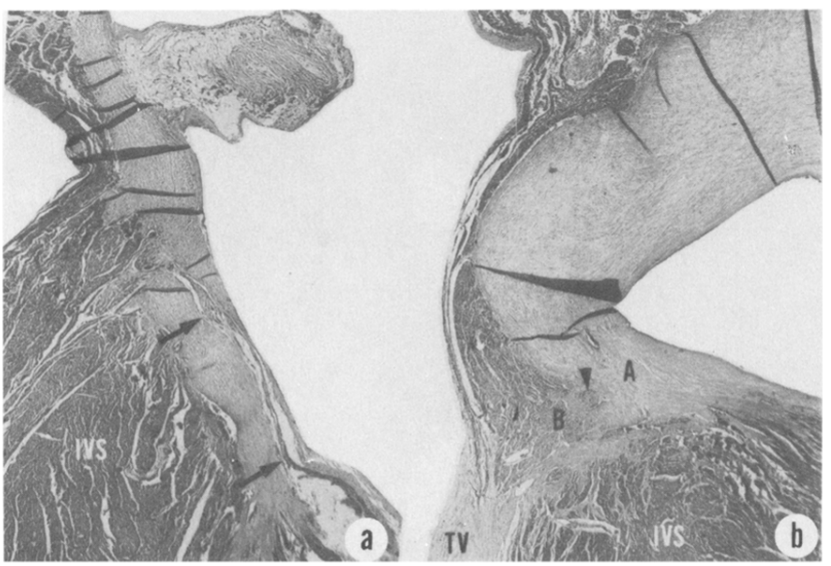

Figure 3. Case 3. Two light microscopic sections from the heart. **a**, There is fibrosis surrounding the left bundle branch (**arrows**). **b**, The thickened anulus fibrosus (A) shifts the penetrating atrioventricular bundle (B) to the right side of the septum. Small clusters of bundle cells are seen isolated in this connective tissue of the anulus (**arrowhead**). Abbreviations as in Figure 1. (Magnification ×20, reduced by 30%.)

eral days before death, the infant had had an upper respiratory infection. Although there was respiratory congestion and focal, mild acute bronchopneumonia, the cause of death was listed as sudden infant death syndrome.

Histology. The lateral AV junctions were normal with atrial myocardium separated from ventricular myocardium by a well formed anulus fibrosus. Distally, the AV junctional tissues appeared structurally normal. The distal bundle of His gave rise to the bundle branches in a normal fashion. Proximally, the anulus fibrosus was thickened and shifted the penetrating and proximal bundle as well as the AV node to the right. Clusters of bundle and nodal cells were caught in the anulus and appeared to be isolated in this overdeveloped structure (Fig. 4). In fact, it appeared that some connections between the node and bundle might have been severed by the overgrowth of the fibrous ring tissue. Proximally, the AV node appeared normal, with the transitional zone of cells between the atrial myocardium and the node in the normal position.

Case 5. This 3 month old Hispanic male infant died suddenly one morning in December. There were signs of slight pulmonary congestion and dehydration, but not of a severity to cause death. The cause of death was listed as sudden infant death syndrome.

Histology. Morphologic examination of the lateral AV junctions revealed that they were normal, as were the distal extensions of the septal AV junctional tissues. However, in the region where the AV bundle penetrated the anulus fibrosus, some thickening was noted. As in Case 4, small clusters of nodal and bundle cells became isolated in the region of the enlarged anulus. In the rest of the junction, the specialized conducting tissues including the transitional zone were morphologically normal.

Case 6. This black male infant died suddenly of unexplained causes 5 weeks after birth. He had had a cold a few days before death in December, but was in good health on the day before death. He died in the morning. There was some congestion in the respiratory system, but it was not severe enough to cause death. At autopsy the cause of death was listed as sudden infant death syndrome.

Histology. As described for Cases 4 and 5, the morphologic features of the anulus fibrosus in the lateral AV junction were normal. In addition, the distal septal junctional tissues were also normal. As in the two previous cases, the only variation from normal structure of these junctional tissues was a slightly thickened anulus in the region where the AV bundle penetrated and then joined the node. There were small clusters of isolated bundle and nodal cells in the anulus, but otherwise the specialized conducting tissues were morphologically normal.

Case 7. This 3 month old black male infant died suddenly one morning in December. Although there was a history of diarrhea and dehydration, the autopsy listed the cause of death as sudden infant death syndrome.

Histology. Examination of the heart revealed structurally normal lateral AV junctions. The junctional tissues, including the specialized conducting tissues of the heart, and the anulus fibrosus were morphologically normal except for a slight amount of fibrosis around the origin of the left bundle branch.

Discussion

Morphologic findings. The major finding of this study is that the AV junctional tissues displayed three distinct types of morphology in infants who died from sudden infant death syndrome. Cases 1 and 2 displayed marked variations from the normal structure of the connections between the atria and the ventricles. The most significant of the variations was the presence of an accessory pathway. In both cases,

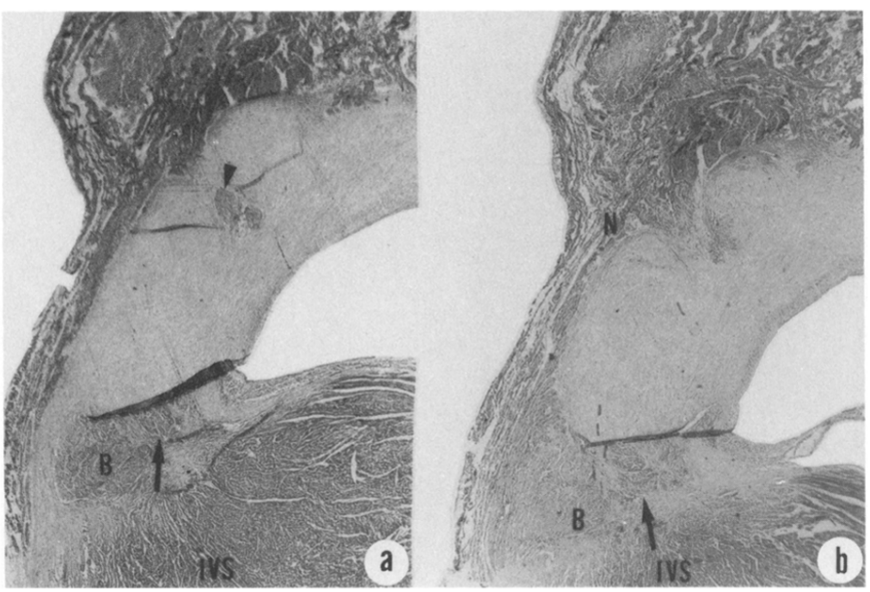

Figure 4. Case 4. Two light microscopic sections from the heart. **a**, The anulus fibrosus (A) is thickened and there are clusters of atrioventricular bundle cells isolated within the anulus (**arrow**). Atrioventricular nodal cells that end blindly in the anulus (**arrowhead**) are also seen. **b**, The anulus shifts the node (N) and bundle (B) to the right side of the septum. Again, isolated clusters of atrioventricular bundle cells (**arrow**) can be seen. The origin of the atrioventricular nodal cells described in **a** is also seen. (Magnification ×20, reduced by 30%.)

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this pathway was a direct connection between the atrial and ventricular myocardium in the septal region. In addition, in Case 2 there were also fasciculoventricular accessory connections. The second group of hearts displayed immature junctional tissues with clusters of AV nodal and bundle cells trapped in a well developed anulus fibrosus. In Cases 3 through 6, the immaturity of the AV junctional tissues, in addition to the well developed anulus fibrosus, were the only variations from the normal histologic features observed. The final group (Case 7) consisted of a heart that displayed virtually normal anatomy with regard to the junctional tissues.

Accessory pathways. The results of this study are consistent with several that preceded it (13,15). In a study of 15 hearts from children who died of sudden infant death syndrome, 1 heart also had an accessory pathway (15). In another study of sudden unexpected death (13), a child with abnormal feeding behavior and cardiac rhythm disturbances died. Subsequent histologic study revealed two accessory pathways between the left atrial and left ventricular myocardium. In addition, the heart of this infant had an atriofascicular bypass tract. There are numerous reports of accessory pathways correlated with sudden cardiac death (17–21), and it is entirely possible that some sudden deaths in infants could result from atrial fibrillation associated with accessory pathways, as in the case of Wolff-Parkinson-White syndrome.

The point can be made that there are probably many factors that can cause sudden unexpected death in any age group including infants. These factors may work together or alone to cause death. In the present study, there were no antemortem findings, so that a direct knowledge of cardiac rhythm disturbances before death was not known. The most that can be deduced from the results of this study is that they demonstrate morphologic abnormalities in the tissues that connect the atria and the ventricles.

Persistent fetal dispersion of AV node or bundle. In Cases 3 through 6, the findings are much more difficult to interpret. The clusters of AV nodal and bundle cells suggested that, at least in some cases, nodal-bundle connections may have been severed. Others (8–10) have described such morphologic features in infants who died suddenly of unexpected causes, and they have suggested that this fetal dispersion may cause sudden death in some cases. However, other investigators (4,22) have thought that these morphologic features were simply those of the typical structure of the conduction tissues in the neonate. In one study (12), focal lesions were found in the region of the AV junctional tissues from hearts of infants who died suddenly, and it was suggested that these lesions might contribute to cardiac functional instability and possibly arrhythmias. In an extensive study (16) of 50 infant hearts, including 26 from infants with the diagnosis of sudden death, it was found that fetal dispersion of the AV node and bundle occurred in both groups of hearts. There was no sign of cell death or degeneration in either group. Thus, it is difficult to say whether there is any possibility that the clusters of AV nodal and bundle cells caught in the anulus fibrosus can result in cardiac functional abnormalities. In the absence of focal lesions or degenerative changes, it is most likely that these isolated cell clusters are benign.

From the present findings, it is evident that there is a maturation that must take place during the postnatal period if the anulus is to assume its adult form. The developmental process by which this occurs is poorly understood and has not been extensively examined. It has been found that different glycosaminoglycans can effect myogenesis (23); this is pertinent in that the location and extent of accessory pathways may be the result of cellular events that go awry. An important question posed quite clearly by James (24) pertains to the mechanism by which the clusters of AV conduction tissue found in the neonate undergo orderly reabsorption. The dissolution of accessory pathways and the process that this entails is also a significant question. Some have suggested (25) that the postnatal development of the anulus will eventually sever these pathways. However, other investigators (20) do not believe that the maturation of the anulus is important in eliminating accessory pathways, but they fail to suggest an alternative.

Sudden infant death. Guntheroth (7,26), responding to a prospective study by Schwartz et al. (27), suggested that there is increasing agreement that the major cause of sudden unexplained death in infants is apnea. In his editorial (26), he suggested that the long QT interval may produce some early deaths as might other arrhythmias. However, he believed that the small number of deaths due to arrhythmias would not account for the majority of deaths. We would agree with this, especially if the second group of cases that we examined turned out to have the normal morphology of the postnatally developing heart. In our study, only two of the seven infants would be possible candidates for sudden death resulting from abnormal cardiac morphology. It does appear, though, that a small yet consistent number of sudden infant deaths may be related to the observed cardiac abnormalities, and further study of this group is necessary.

Underlying morphologic abnormalities. Studies such as those by Anderson et al. (28), in conjunction with our study and others like it (13,15), could provide us with quantitative data on which to base the frequency of those cardiac anatomic abnormalities that might lead to sudden infant death. Studies on the septal AV junctional tissues plus the lateral junctions have found that, of the 23 hearts examined in two other reports (13,15) and in ours, 4 have had an accessory pathway. This represents much too small a sample on which to base any substantive quantitative conclusions, but it might represent the upper limit on the number of infants who die suddenly and unexpectedly and have morphologically apparent cardiac abnormalities such as an accessory pathway. Another factor to consider is the presence of abnormalities in the anatomy of the sinus node, and although evidence

suggests that this structure may not often be the site of a lesion that could be linked to sudden infant death, certainly lesions in this region could cause sudden death (29). In conjunction with this type of study would be an examination of the coronary arteries for lesions that could cause narrowing of these arteries; lesions that could cause narrowing of these arteries also have been linked with sudden death (30).

Cardiac arrhythmias. If the results of future studies do find that a small but substantial number of sudden infant deaths could be the result of arrhythmias caused by accessory pathways, then testing for Wolff-Parkinson-White syndrome could be useful. This syndrome is more clearly demonstrated when conduction time is slowed and, depending on the location of the pathway, the standard electrocardiogram may not show signs of this arrhythmia (31). Therefore, prospective testing that may be needed in the future might include slowing conduction time by using manuevers such as the dive reflex. It is interesting that the dive reflex has also been implicated in the generation of apnea and in other arrhythmias (7,32). This may become a very useful test not only to elucidate arrhythmias generated by accessory pathways, but also under careful monitoring this test could be used to examine apneic episodes.

Significant changes in the morphology of the AV junctional tissues during the postnatal period may explain why there has been little success with routine infant monitoring and predicting which infants are potential candidates for sudden infant death (33–38). Because there are dynamic structural changes in the AV junctional tissues after birth, it is possible that early studies would not show rhythm disturbances, but that subsequent maturation may cause alterations in the conducting tissues and subsequent anomalies might be lethal.

Implications. It was thought that perhaps the heart in those infants who were classic high risk candidates for sudden infant death syndrome (3–7) might fall into one of the groups of hearts as classified on the basis of our proposed system. However, this did not turn out to be the case. Patient 2 was a classic sudden infant death syndrome victim: he was 3 months old, black and male, had prior respiratory infection and a family history of sudden death. The one exception was that he died in the summer. Patient 1, on the other hand, was 4 months old, white and male, had no prior respiratory infection, no family history of sudden death and died in the summer. He would not have been classified as a high risk candidate. So there was no consistent type of infant who would be found in the first group of cases with accessory pathways. In the second group of infants with the immature cardiac junctional tissues, there was also no consistent set of characteristics that described this group. It remains that until there is definitive information on the cause of sudden infant death syndrome, a complete autopsy of infants who die of sudden unexplained causes should be performed whenever possible (2). Included in this study would be an examination of the cardiac AV junctional tissues, including the lateral AV junctions (17), which is done on serial sections of these critical and dynamically changing regions of the postnatally developing infant heart.

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