
The Sinus Node in Sudden Infant Death Syndrome

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SUMMARY The sinus node (SN) was examined histologically in 30 infants diagnosed with sudden infant death syndrome (SIDS) and in 18 age-matched controls who died of known causes. Location, size and organization of the SN did not differ significantly in the two groups. Petechiae involved the SN region in 20% of SIDS and 17% of control infants and probably do not represent a primary event. In three SIDS infants (10%), intimal lesions reduced the lumen of the intranodal SN artery by 63–83% in cross-sectional area. These resembled the intimal thickening frequently observed in main epicardial coronary arteries of infants. Whether the vascular alterations in these three cases had adverse effects upon SN function is unknown.

THE PRIMARY CAUSES of the vast majority of sudden unexpected deaths in infancy (SIDS) remain unknown. Sudden cessation of some vital physiologic function, such as respiratory or cardiac arrest, continues to be a major hypothesis.† Studies of the cardiac conduction system in SIDS are usually directed to the atrioventricular node and His bundle.‡-7 The sinus node (SN) in SIDS has been described as anatomically normal.‡-4, 7 Small hemorrhages have been common in atrial musculature and perinodal autonomic ganglia, occasionally occurring within the SN itself.‡-6, 7 Similar hemorrhages are equally common in controls. James noted degenerative changes in the perinodal autonomic ganglia associated with the hemorrhages.3

We examined one infant with a documented conduction disturbance who died unexpectedly without demonstrated cause and who had an atrioventricular bypass tract. This experience and the disparate findings in the literature prompted a new analysis of the cardiac conduction system in SIDS victims. Studies of the SN are reported here.

Materials and Methods

The SN was examined histologically in 30 SIDS victims and 18 age-matched controls at Children's Hospital Medical Center, Boston, who died from 1975–1980. SIDS was defined by sudden and explained death in a previously healthy infant younger than 18 months of age. (Two SIDS infants were initially resuscitated, but one died 6 hours and the other 4

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days later.) The control group of 18 infants had an equal sex distribution and ranged in age from 1 day to 18 months. In the control group, two patients had disseminated infection, probably viral; two had epidermolysis bullosa; two had multiple congenital anomalies; and one patient each had meningitis, acute bronchiolitis, aspiration pneumonitis, bronchopulmonary dysplasia, purpura fulminans, hemophilia, Wilms' tumor, hepatoblastoma, infantile polycystic renal disease, trauma, propionic acidemia and Zellweger's syndrome.

At autopsy, in all cases except one, the heart was fixed in 10% buffered formalin. The entire superior vena cava–right atrial junction was removed as a ring of tissue 2.5 cm in height. At the time of paraffin embedding, the tissue ring was collapsed in an anteroposterior plane to provide a relatively thin rectangular tissue block which was serially sectioned at 10 μm. Forty-five cases were sectioned in the sagittal plane and two in the horizontal plane. All sections were retained and every fiftieth and adjacent sections stained with hematoxylin-eosin. After localization of the SN, all adjacent sections of the complete SN were stained with hematoxylin-eosin and modified Movat's pentachrome. Sections in selected cases were submitted for periodic acid-Schiff and reticulin stains. In one SIDS case, the tissue block was removed from the fresh heart, quick-frozen, and 10-μ cryostat sections were cut at different levels, primarily for histochemical demonstration of cholinesterase.

The maximum width (diameter) of the SN in a plane perpendicular to the endocardial surface of the superior vena cava was measured by ocular micrometry and plotted vs age. The internal and external diameters of the SN artery within the midsegment of the SN were measured. The ratio of internal to external diameter of the SN artery (ID:ED) was calculated and plotted vs age. The coordinates of all measurements were subjected to linear regression analysis for SIDS and controls separately.

**Results**

The SN in all cases was situated subepicardially anterolaterally at the superior vena cava–right atrial junction in the sulcus terminalis (fig. 1). The centrally placed artery was surrounded by a prominent collagenous collar, in contrast to the sparse collagenous framework in the remainder of the SN. The nodal cells formed a woven network with occasional fibers extending to the media of the SN artery. The transitional fibers at the periphery of the node were enlarged and blended with the adjacent atrial musculature. A few lymphocytes, disposed around the ganglia and within the epicardial fat, were common in both groups.

The maximum width of the SN was similar in both groups (fig. 2), with no statistically significant difference between the respective regression lines (p < 0.05).

Petechial hemorrhages occurred in six SIDS cases (20%) (perinodally in five and intranodally in one), and perinodally in three controls (17%). No necrosis, nodal cell degeneration, replacement fibrosis or hemosiderin deposits were observed in the SN in the SIDS group. In the control group, the SN was involved twice as a part of a generalized myocarditis, presumably viral, and once by extension of a fibrinopurulent pericarditis.

The SN artery in the SIDS group entered the SN laterally in 21 instances and medially in nine, not differing significantly from the control group with corresponding frequencies of 13 and five, respectively. There was a moderate variation in SN artery size in both groups.

**Figure 1.** The sinus node (SN) (interrupted line) in its medial two-thirds sectioned in a horizontal plane. The SN artery is centrally placed. RAA = right atrial appendage; SVC = superior vena cava. Movat stain; magnification × 2.

**Figure 2.** Maximum width of sinus node related to age in sudden infant death syndrome (SIDS) and control infants with regression lines.
Intimal thickenings in the intranodal SN artery, similar to those in the main coronary arteries of most infants, were present in approximately three-fourths of SIDS and control infants and were even more frequent in its extranodal segment. These intimal thickenings were primarily musculoelastic membranes associated with a discontinuous internal elastic lamina and were of minor degree (figs. 3D and 4B).

In three SIDS cases, almost the entire intranodal course of the artery was involved (narrowed) by intimal lesions within the spectrum of those commonly observed in main coronary arteries of infants. Figures 3A and 3B depict the SN artery of two SIDS infants with lumina constricted by intimal hyperplasia of smooth muscle and elastic fibers. Little internal elastic lamina remained and the innermost intima displayed edema with a moderate amount of acid mucopolysaccharides on Movat's stain. In the third SIDS infant (fig. 3C), the intima was markedly expanded by ground substance staining weakly for acid mucopolysaccharides. In these three infants the luminal cross-sectional area was reduced by 85%, 65%, and 63%, respectively. One control infant had prominent musculoelastic intimal cushions (fig. 4A).

The SN arterial ID:ED ratios had a wide range in SIDS and control infants (fig. 5) reflecting primarily the variable size of the artery. There was no statistically significant difference between the regression lines for the two groups ($p < 0.05$). In the three SIDS and single control infants with major (prominent) SN arterial narrowing, the ID:ED ratios exceeded 2 standard deviations from the means.

Histochemical cholinesterase staining of the SN in one SIDS infant revealed strong positivity in nodal cells, autonomic ganglia and nerves and weaker positivity in atrial muscle. The results are similar to those observed in our laboratory in infants who die from other causes (not included in this study). Similar results have been described by Anderson in the SN of SIDS and controls quoted by Lie et al. and by James and Spence in the adult SN.

No unusual pre- or postnatal events were recorded for the three SIDS infants with marked intimal lesions of the SN artery. The infant whose SN artery is shown

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**Figure 3.** Intimal lesions in the sinus node (SN) artery of four infants who died with sudden infant death syndrome (SIDS). (A and B) Intimal hyperplasia of smooth muscle, elastic fibers and fibroblasts with increased ground substance. Internal elastic lamina is only focally preserved. Movat stain; magnification $A \times 110$; $B \times 160$. (C) Intimal expansion by ground substance, fibroblasts and smooth muscle cells. Movat stain; magnification $\times 210$. (D) Typical low-profile musculoelastic intimal cushions observed in SN artery of most SIDS infants. Movat stain; magnification $\times 325$. 
thickenings in the coronary arteries and the aorta and its abdominal branches were not greater than usual for infants at these sites.

Discussion

The SN in SIDS has been described as structurally normal in previous reports, although vicinal petechiae have been common. In the present study the SN was normal in location, size and organization. Petechiae were present in 20% of SIDS and 17% of control infants and probably do not represent a primary event.

Focal thickening of intima is common in the coronary arteries of infants. Similar but mild changes in SN arteries were common among both SIDS and control infants in this study. In four infants, three SIDS and one control, intimal lesions narrowed the luminal cross-sectional area of the SN artery by 63–83%. The lesions were more than focal, involving most of the intranodal course of the artery, and differed in quality: Three involved musculofibroelastic hyperplasia and one primarily ground substance and edema.

Intimal thickenings in main coronary arteries of infants are considered by some to represent a physiologic response to hemodynamic stress, resulting from a steep pulse wave, prominent pulsation from lack of adjacent soft tissue support, and tethering at origins of large branches. Occasionally, the intimal thickenings appear excessive. The reasons for the excessive intimal thickenings in the SN arteries of the above four infants is unknown. Hemodynamic stress, whether mediated by autonomic imbalance or not, might cause such arterial changes. Cardiac autonomic imbalance has been a leading hypothesis as a substrate for SIDS. An abnormality of the autonomic system could well have been present in addition to hypoplasia of multiple cranial nerves in the control infant.

The significance of the SN arterial narrowing in the

in figure 3B was initially resuscitated but died 6 hours later. ECGs during this period showed irregular sinus rhythm, elevated ST segments, inverted T waves, and a corrected QT interval not exceeding 0.42 second. Intermittent episodes of ventricular tachycardia were of the torsade de pointes variety. All three infants (two females and one male) had focal intimal thickening in the main coronary arteries and in the aorta and its large abdominal branches, but not greater than usual for infants at these sites. Increased muscularity of the pulmonary arterial circulation, as has been described in most SIDS victims, was present in the two others. One of the three infants did not have thoracic visceral petechiae.

The control infant with marked intimal thickening in her SN artery had hypoplasia of multiple cranial nerves and diaphragmatic paralysis, necessitating continuous mechanical ventilatory support. She suffered a fatal cardiac arrest at 7 months of age. The pulmonary arteries exhibited medial hypertrophy, but no peripheral extension of muscle was present. Intimal
three SIDS infants is unclear. No histologic evidence of recent or remote injury of nodal cells was seen. In view of its anastomoses with other atrial arteries, a localized narrowing of the SN artery is of uncertain significance. James described infarction of the SN as a regular finding in hearts of patients who developed atrial arrhythmias during acute myocardial infarction. A main coronary occlusion was found proximal to the origin of the SN artery in all instances with severe atherosclerosis or occlusions in the other main coronary arteries. Ligation of the SN artery in the dog does not result in atrial arrhythmias, possibly because an otherwise healthy coronary circulation permits collateral blood flow. One might expect that if narrowing of the SN artery does have adverse effects upon the SN, these would more likely occur if the intranodal arterial segment were affected, as in the three SIDS victims in our study.

Abnormality of the SN artery has been described in a wide variety of diseases. Intimal proliferation has been observed in scleroderma heart disease and congenital homocystinuria. Fibromuscular dysplasia of the SN artery has been reported in a variety of disorders, including primary pulmonary hypertension, Marfan's syndrome, asymmetric hypertrophy of the heart and congenitally deaf children with a prolonged QT interval. It has also been described in children and young men who died suddenly and unexpectedly and whose deaths were otherwise unexplainable.

Absence of morphologic evidence of injury to nodal cells in the three SIDS victims does not preclude the possibility that temporary nodal dysfunction may have resulted in an arrhythmia, conduction disturbance or momentary cardiac inadequacy with a fatal outcome. Emery estimated that 10% of SIDS deaths could be attributed to primary cardiac arrhythmia, which corresponds to the percentage of SIDS victims in our study with severe intimal lesions in the SN artery.

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