THEORIES OF CARDIOVASCULAR CAUSES IN SUDDEN INFANT DEATH SYNDROME

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The sudden infant death syndrome (SIDS) is defined as sudden death in infants, unexpected by history, for which no cause is found at autopsy. The peak rate of SIDS occurs between 2 and 3 months of life, and it is uncommon before 1 month and after 6 months (1). Survivors of episodes that seem to be life threatening (apparent life-threatening events) are usually called near-miss for SIDS, or simply near-SIDS. Although the relation between these live infants and those who die suddenly is disputed, there are no diseases known to humans that have no survivors (2). Without these living subjects very little can be determined about the pathophysiology of SIDS.

In considering the cause of sudden death at any age, it is worth beginning with the final pathway to death, apnea versus arrhythmia. Froggatt et al. (3) asserted that identification of this final pathway was the outstanding problem in the study of SIDS. In this process, it is necessary to distinguish between primary and secondary—or terminal—disorders; ventricular fibrillation secondary to prolonged hypoxia should be distinguished from that resulting from the Romano-Ward syndrome. This editorial review addresses the possibility that SIDS is due to a primary cardiac disorder.

**Adult Sudden Death**

In the adult, cardiac arrhythmias, either ventricular fibrillation or asystole, are the cause of 90% of deaths attributed to heart disease (4). However, many adults survive these "apparent life-threatening events," allowing documentation of arrhythmia as the cause of the event. The infant with an apparent life-threatening event or near-SIDS rarely demonstrates an arrhythmia, but Schwartz (5) rejected the relevance of near-SIDS infants to infants with actual SIDS, contending that infants are very unlikely to survive a silent arrhythmia, ignoring the survival of adults with arrhythmias and serious cardiovascular disease. Surawicz (6) estimated that <5% of adults with ventricular arrhythmias would die suddenly during the first year after infarction. In a group of adults who died suddenly, only 20% to 25% were without prior signs or symptoms of coronary artery disease (7).

Similarly, arrhythmias during prolonged sleep apnea in adults tend to be relatively benign unless there is heart disease. Otsuka et al. (8) found simple bradyarrhythmias associated with apneic episodes lasting >20 s, whereas ventricular arrhythmias occurred only in patients with old myocardial infarction, coincident with apnea of ≥40 s duration.

Because SIDS victims have no evidence of heart disease at autopsy, if arrhythmias were a common cause of SIDS there should be many near-SIDS alive for documentation of their arrhythmias. Froggatt (9) explicitly acknowledged this consideration as contrary to his own cardiac hypothesis for cot death: "...without demonstrable ventricular arrhythmias in live infants we must consider the (cardiac) theory at best unproven."

**Sudden Death in Infants With Known Cardiac Disorders**

In the pediatric age group, 75% of the sudden deaths attributed to arrhythmias occur in patients with relatively severe heart disease who are symptomatic (10) and therefore excluded from the category of SIDS by definition. Patients with primary arrhythmias, without other heart disease, rarely die in infancy, suddenly or otherwise. Of 90 infants with pre-excitation who presented with supraventricular tachycardia in the first 4 months of life, only 3 died, all of whom had congenital heart disease; only one sudden death occurred in a 1 month old infant (11).

Even ventricular arrhythmias are not as emergent a problem in infants as when they occur in the adult (12). As with supraventricular tachycardia in infants, ventricular tachycardia does not usually cause sudden death without other abnormalities; it is more likely to cause congestive heart failure, with tachypnea, tachycardia, grunting respiration, pallor and cold perspiration, obvious to most mothers.

At the other extreme of heart rate, complete heart block in infants with a heart rate of <½ of normal commonly permits normal growth and activity, and neither syncope nor
congestive failure is likely without an additional cardiovascular lesion.

Hereditary forms of the long QT syndrome are usually discovered in childhood after an asymptomatic infancy. In the families with Romano-Ward syndrome that we followed up (13), no one had onset of symptoms before 5 years of age. Among all 203 cases of long QT syndrome reported by Schwartz et al. (14), only 8 infants (4%) had syncope in the first year and only 2 (1%) died in infancy.

Without clinical grounds for diagnosing heart disease, James (15) suggested that a number of victims of SIDS died of arrhythmias, based on the histologic features of the cardiac conduction system. However, he found the same changes in control infants who died of causes other than SIDS. Valdes-Dapena et al. (16) argued that there was no basis for invoking a fatal malfunction of the conduction system.

Prevalence of Arrhythmias in Infants

In 1980, Southall et al. (17) summarized their results from 24 h tape recordings of the electrocardiogram (ECG) and respiration in 50 healthy term infants. They found that 28% had a junctional escape rhythm with sinus bradycardia, 10% had only solitary supraventricular premature beats and 4% had solitary ventricular premature beats. Episodes of bradycardia were found with all episodes of apnea >15 s duration. In 1983, they (18) summarized the results of 24 h ECGs on 9,000 infants who had prospective recordings in the first 6 weeks of life. Arrhythmias were observed in only 1% of these normal infants. Of the 29 infants who subsequently died of SIDS, only 1 had an arrhythmia (occasional ventricular premature beats). None of the 29 had pre-excitation or prolonged QT interval.

Studies of near-SIDS infants (19), based on home ECG monitoring, revealed that none had ever required defibrillation or cardiac massage. Montague et al. (20) used 24 h continuous ECG monitoring in nine near-SIDS infants, all of whom had required resuscitation from an episode that was judged life threatening. None of them had excessive bradycardia, except with apnea, or arrhythmias, and all had a normal QT interval.

Guilleminault et al. (21) reported on eight infants with near-SIDS who demonstrated arrhythmias with non-rapid eye movement (REM) sleep, predominantly “sinus arrest.” The infants did not require any intervention beyond stimulation to restore respiration, and they all survived without sequelae.

Theories of Abnormal Cardiovascular Reflexes

In the first description of near-SIDS, in 1963 (22), bradycardia accompanying apnea was reported. In 1966, Wolf (23) proposed that this combination of apnea and bradycardia represented a dive reflex and that a disorder of this reflex might cause SIDS. In fact, our group (24) found a high prevalence of bradycardia in premature infants compared with full-term infants and speculated that the bradycardia might indicate some form of “instability of cardiovascular control,” and thus a greater susceptibility to sudden infant death. However, the secondary nature of bradycardia after apnea was documented in premature infants by Daily et al. (25) in 1969. Subsequently, on the basis of experiments in baby monkeys, we (26) concluded that the sinus bradycardia was a conservative feature of the dive reflex.

Additional cardiovascular reflexes that have been suggested as possible explanations for SIDS include the oculocardiac reflex (27), stimulated by pressure on the eyeball in the prone position in infants. The Belgian SIDS group (28) also implicated the oculocardiac reflex in SIDS; they reported that the period of asystole after ocular compression in near-SIDS infants was significantly longer than that in control infants, indicating a possible role for “vagal hypersensitivity” in SIDS.

The Long QT Syndrome and Developmental Hypothesis

It is understandable that a disorder capable of causing sudden death in adults and children that leaves no consistent autopsy findings would be suspected of causing sudden infant death (29). In 1976, the group at the National Heart Institute (30) announced that they had found a prolonged QT interval in a significant number of parents of SIDS victims (26%) and in 39% of siblings of SIDS patients. They concluded that there was an autosomal dominant pattern of inheritance and that a considerable proportion of SIDS might be explained by the long QT syndrome.

Kukolich et al. (31) compared the QT interval in first degree relatives of victims of SIDS with that in control subjects. There was no significant difference, thus ruling out the hereditary long QT syndrome as a significant factor in SIDS. If either the Jervell and Lange-Neilsen syndrome or the Romano-Ward syndrome played a major role in SIDS, the expected recurrence rate of SIDS would be as high as 25% to 50%, whereas the recurrence rate of SIDS in families is only ≤2%. Kukolich et al. (31) criticized the failure of Maron et al. (30) to include control observations.

Schwartz (32) proposed in 1976 that there might be a transient, developmental condition with prolonged QTc that created a susceptibility to SIDS, distinct from the genetic syndromes. He and his co-workers (33) attempted to support the developmental hypothesis by showing a parallel course of prolongation of the QTc interval and increasing age between 4 days and 2 months, the latter near to the age of peak incidence of SIDS. Although they claimed a highly significant difference between the two means, the actual
difference was only 10 ms (5), revised later to 12 ms (34); the difference between the means was actually less than a single standard deviation for either age group and equal to or less than the interobserver or intraobserver variability (35,36).

A conceptual problem is apparent in the experimental design of the studies of Schwartz and his group. Since the first month of life is generally spared by SIDS, his theory would predict that the QTc interval in the first month would remain shorter than the QTc interval at 2 months of age. His protocol has never included measurements in the first month, except for the records at 4 days of age, although this omission was pointed out early in the data collection period (37). Fortunately, Weinstein and Steinschneider (38) have reported on the QTc interval at 1 week and at 4 weeks in almost 1,000 normal infants; the QTc interval increased, just as Schwartz et al. (33) found when comparing values at 4 days and at 2 months of age. The time course of increasing mean QTc interval then does not parallel the time course for SIDS. Even the concept of the developmental long QT hypothesis, which inherently assumes that SIDS is related to immaturity, is inconsistent with the hiatus for SIDS in the first month of life. If SIDS were a simple developmental phenomenon, the premature infant, who has one of the highest risks for SIDS, should have more prolongation of the QTc interval than does the full-term infant. That is not the case in the 1982 data of Schwartz et al. (32); the QTc interval at 2 months of age for preterm infants was actually shorter than that of full-term infants.

Whether Milan is a fair test site to establish normal values for the QTc interval in infants is uncertain, because there seems to be an unusual concentration of patients with the Romano-Ward syndrome around that center (39). Nevertheless, the upper limit of normal reported from the studies of Ambroggi et al. (39) is in agreement with values from other centers; 0.45 s for infants based on 2.6 SD of the population. However, using this population with a high rate of the Romano-Ward syndrome to determine rates of sudden death in infants may create a more important problem. In his 1987 report (34), Schwartz listed 9 infants who died of SIDS among 8,000 infants available for follow-up; 6 of the 9 had a "markedly prolonged QTc," which he defined as exceeding the mean by >2 SD. (In 1982 he had defined "markedly prolonged" as >3 SD.)

Other prospective studies do not confirm Schwartz's data or conclusions. Of the 1,000 infants studied prospectively by Weinstein and Steinschneider (38), 8 subsequently died of SIDS; none had prolongation of the QTc interval relative to findings in the control infants. In fact, the future SIDS infants had a shorter mean QTc value than that of the control infants, although the difference was not significant at the 5% level.

Southall and his colleagues (18) in their initial prospective study of the QTc interval employed Holter-type magnetic tape recorders. They recorded 24 h tapes on 6,914 full-term and 2,337 pre-term infants during the first 6 weeks of life. Subsequently, 29 of these infants died of SIDS. None of these infants showed abnormal prolongation of the QTc interval, based on comparison with values in their control population, and only one had an arrhythmia (single ventricular extrasystoles). Their second study (36) was performed using conventional ECG recorders; a total of 7,254 newborn infants were enrolled. The SIDS cases were compared with control cases stratified by age. In addition to correcting for rate with Bazett's formula, two other methods for normalizing data were used based on the RR intervals. Of the 15 infants who subsequently died of SIDS, only 1 had a QT or QTc interval that exceeded the 95th percentile for their control group. There was no significant difference between the mean values in the SIDS and control infants. On the basis of the individually matched RR method, none of the SIDS infants had a prolongation of either the QT or the QTc interval.

Patient populations that have the highest known rate of SIDS, the near-SIDS (1), have been examined for prolonged QTc interval in several centers. No prolongation of the mean QTc interval has been found, nor arrhythmias, the lethal link between delayed repolarization and SIDS (20,40–42); the mean QTc interval for infants with near-SIDS was actually shorter.

Sadeh and colleagues (43) announced at a news conference in 1987 that they had reanalyzed Southall's tape recordings and discovered that "in some babies with SIDS the ability to shorten the QT interval as the heart rate increases is impaired." They explicitly applied Bazett's correction of the QT interval (44) to nonsteady states, ignoring two generations of reports (45,46) that the QTc interval would not reflect rapid changes in the RR interval. This "failure," as Sadeh et al. called it, can be seen in their Figure 3; the record begins with a heart rate of approximately 170 and slows abruptly to 146 beats/min. The QT interval very slowly increases to a new steady state, requiring almost 2 min. Sadeh et al. (43) appear to be surprised by the dissociation between the heart rate and the QT interval with a rapid change in rate, and concluded that this was evidence of "impaired cardiac repolarization." Their summary that "these observations are consistent with the hypothesis that relatively prolonged cardiac repolarization may predispose such babies to ventricular arrhythmias," may be judged by their failure to find a single arrhythmia in any of these 6 h tapes, and by the fact that the mean QTc interval of the SIDS group was shorter than that of the control group. Only when they substituted a new exponent, 0.134 instead of Bazett's 0.5, did they find a longer "corrected QT" for the SIDS group, but the difference of the means was not significant at the 5% level. To equate a failure of Bazett's exponent to predict the QTc interval from nonsteady state heart rate with the more ominous sounding "prolonged QT interval" is a serious exaggeration.
Other Cardiovascular Theories

A final cardiac hypothesis returns us to two early explanations for SIDS, positioning of the infant during sleep and a thymus death. There is no statistical basis for the claim that the prone position can cause accidental suffocation, and *mors thymica* is only of historical interest (1). However, as late as 1987 Hori (47) theorized that the prone position causes the “heavy” ventricles of the infant to fall forward, kinking against the large thymus, characteristic of infancy, thereby preventing filling of the heart and stimulating an arrhythmia or cardiac arrest. Considering the prevalence of both the prone position and a plump thymus in infancy, Hori’s theory is comparable with the theory that we all die of oxygen toxicity, because there is a perfect correlation between exposure and death. His contribution is unlikely to resuscitate the cardiac theory of SIDS.

Conclusion

There is no statistical basis, with sound and reproducible methods, to support a cardiac theory for the cause of sudden infant death syndrome.

References


