
FEATURES

The quest for the mechanisms of the sudden infant death syndrome: doubts and progress

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THE LEADING CAUSE of mortality during the first year of life, after the neonatal period, is the sudden infant death syndrome (SIDS), also known as cot or crib death.¹ Its incidence is close to 2 per 1000 live births in most countries, although in some, e.g., the Scandinavian countries, it is markedly lower. It is usually defined as the sudden death of any infant or young child, which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause for death. Because of the high incidence, the catastrophic impact on the affected families, the mystery still surrounding these deaths, and the unsolved scientific problem, SIDS represents a major challenge for contemporary medicine.

Prevention of a given event, sudden death in this case, requires an adequate understanding of the mechanisms involved. With regard to SIDS, these mechanisms remain elusive. Here I will discuss some of the actual difficulties and methodologic problems in the research on SIDS and then analyze the respiratory and cardiac theories. The latter will be presented in greater detail, which is not meant to reflect its more prominent role, but rather my area of expertise and my role as one of its proponents.²

A difficult target. Among the many intriguing aspects of SIDS, one certainly is the mixture of hard and soft scientific data on this disorder, as evidenced by critical review of the published studies. This results largely from the involvement — quite unusual in medicine — of investigators with such diverse backgrounds that all too often the interested audience does not have the expertise necessary to recognize potential weaknesses and to identify wrong conclusions. The remarkable lack of documented information is accompanied by a

huge number of proposed theories. It is worth recalling that, as stated by Peter Froggatt, “the theories of the accredited scientist and of the quack are alike to the eyes of the gullible beholder.”³

There is a consensus that SIDS is multifactorial, i.e., that different mechanisms and causes are involved; this, however, does not mean that they are all equally important. Indeed, it is very likely that the majority of the proposed hypotheses accounts for a small fraction of SIDS and that most of SIDS deaths are the result of a few critical mechanisms. The respiratory and cardiac disorders are, on logical grounds, probably those involved more often.

General problems. Since SIDS is a disease in which the initial event is the discovery of a dead infant, it comes as no surprise that the more extensive investigations have been in the areas of epidemiology and pathology. While much detailed information is available in most of the reviews on SIDS,^{1,4} two findings seem to be the most practically relevant to the understanding of the mechanisms involved. The most striking and critical epidemiologic finding is the unique age distribution of SIDS victims, which shows a peak incidence in the second and third month of life, with relative sparing during the first and after the fifth month. Any viable hypothesis for the cause of SIDS must account for its characteristic age distribution. On the other hand, the single most important finding in the extensive pathologic studies of the disease remains the absence of an adequate cause of death at autopsy.

The greatest limitation of epidemiologic studies lies in the fact that the identification of general risk factors, such as birth weight, race, maternal and socioeconomic characteristics, and so on, has almost no value in identifying the *individual* infant at high risk for SIDS. As for any disease characterized by a very low incidence, any risk factor would leave quite a high number of false positives. In the case of SIDS, with an incidence of two in 1000, a factor that would increase the

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risk by even five times would still leave 99% false positives.

The greatest limitation of the pathologic studies lies in the fact that the mechanisms of death proposed by the respiratory and cardiac hypotheses, lethal apnea and ventricular fibrillation, are functional disorders almost never associated with definitive organic or structural alterations whose presence could ensure or whose absence could negate the operation of the deadly mechanism. These studies also suffer greatly for the lack of adequate controls, e.g., healthy infants dying suddenly because of an accident; the definition of "abnormalities" requires that large number of controls be studied to define normality and its range.

The SIDS researchers have to contend with a difficult reality: although anecdotal exceptions exist, the overwhelming majority of SIDS victims die without having undergone a thorough medicophysiology investigation and without a documented record of what happened at the very moment they died. This lack of factual information, at variance with any other disease, explains why so much speculation has been possible on the cause(s) of SIDS. The appropriate answers might be obtained by prospective studies in a huge number of thoroughly evaluated infants, as suggested long ago,² but the organizational and economic aspects represent difficulties that cannot be underestimated.

Specific problems. Some specific difficulties in SIDS research, which are particularly relevant to the respiratory and to the cardiac hypothesis but are valid in general, originate from the use, or rather the misuse, of infants considered at "high risk" for SIDS, including putative "survivors" of SIDS.

The proposal to broaden the SIDS spectrum to include those living infants who have been resuscitated from what otherwise would have resembled sudden infant death gave origin to the concept of a "near miss." The reasons for including the near misses in the SIDS group and the pitfalls of this concept have been analyzed in detail elsewhere.¹ The subsequent occurrence of sudden death in some of these infants (1.4% of approximately 800 cases according to one of the most recent reviews⁵) has prematurely led to the equation: near miss equals SIDS. Several caveats are appropriate here. The infants suffering a near miss represent a mixed population, only part of which has a truly unexplained episode of near death.⁴ The label near miss is most of the time the consequence of a judgment made by understandably anxious parents. A recent study by Krongrad and O'Neill⁶ examined 93 episodes considered by the parents of 20 high-risk infants under continuous monitoring to be true alarms. All the electro-

cardiographic tracings recorded during these episodes were normal, indicating that not even apnea of significant duration had occurred. The authors conclude: "Our data raise questions regarding parental clinical ability to correctly perceive a true near miss episode in most cases and may explain, in part, the lack of consistency noted in previously published physiologic studies of 'high risk populations.'"

A respiratory death is relatively slow and allows a few minutes to observe apnea, cyanosis, and struggle, whereas death by ventricular fibrillation is instantaneous and silent. It is far more likely that a mother will observe her child dying a respiratory than a cardiac death. This will allow her to intervene and to save the infant, creating a new near miss. It follows that infants suffering a near miss would more likely be afflicted with a respiratory than cardiac disorder and it is not surprising that most studies of these infants reveal some respiratory abnormality. As a matter of fact, with the acceptance of the near miss as an integral part of SIDS, apnea became the focus of research. The infants suffering a near miss represent a subgroup at a somewhat higher risk for SIDS (approximately seven times,⁵ and perhaps more for those with repeated episodes) that may provide information highly relevant to the role of respiratory abnormalities in the genesis of SIDS, but they may also constitute a source of quite misleading information if data are uncritically extrapolated to the entire SIDS problem.

These limitations also apply to studies performed in other high-risk infants, such as the siblings of SIDS victims, premature infants, and so on. The main question is the real meaning of "high risk." These groups seem to have an incidence of SIDS below or close to 0.5%,⁷ which, although double that for normal infants, is relatively low. Moreover, this implies that, with a 99% or 99.5% rate of false positives, if 1000 of these infants were studied only five of them would actually become SIDS victims. Conclusions drawn from studies of 30 or 50 such subjects focusing on the absence of a given variable are not scientifically sound. While these may effectively persuade an audience, they have dubious bearing on the SIDS problem.

In the several published studies based on negative findings in small populations of infants "at risk" (for details see Schwartz⁸), there seems to be confusion surrounding the relative importance of positive and negative findings. The presence of a given factor indicates a potential role and what remains to be assessed is the degree of correlation with the occurrence of the event. The absence of the same variable indicates only that it is not present in the particular population under

study. Thus, when the event to be predicted (SIDS death) has a very low incidence, even in the study population supposedly at risk, extrapolation to the general population and particularly to the true SIDS population is difficult.

The respiratory theory. After the rejection of the hypothesis that asphyxia secondary to laryngospasm is a cause of SIDS and given the uncertainties still surrounding the so called "aberrant laryngeal reflexes," certainly the most popular respiratory theory (one that also enjoys the widest general support as the main cause of SIDS) is the "apnea hypothesis."

According to this, SIDS is caused by a sudden spontaneous apnea favored by sleep. Both central and obstructive apnea have been implicated. Central abnormalities in the control of ventilatory muscles during sleep have been suggested, as well as defects in the arousal mechanism involving the reflex response to mild hypercapnia or hypoxia.⁹ As discussed below, apnea may play an important role in SIDS by also favoring a cardiac death. The main support for the apnea hypothesis comes from a series of pathologic findings and from the studies on infants suffering a near miss. An impressive series of studies by Naeye¹⁰ indicated that most SIDS victims had morphologic evidence of "chronic hypoxia," and provided the strongest basis for the proposition that SIDS infants have a number of apneic episodes and eventually succumb to a more prolonged irreversible apnea.

Most of the numerous studies in near miss infants have found a variety of abnormalities in respiratory function. All types of apnea, hypoventilation, insufficient increase in ventilation during exposure to hypercapnia or hypoxia, and other abnormal breathing patterns have been described in this group.⁹ These results, taken together, have strengthened the concept of the apnea hypothesis.

Data that do not support the apnea hypothesis as the major mechanism for SIDS have also been reported. An accurate analysis of more than 800 certified instances of SIDS revealed that only 5% of the victims previously experienced an observed apneic episode.¹¹ In a prospective study Southall et al.¹² recorded the breathing movements for one period of 24 hr during the first 6 weeks of life in 9251 infants; none of the recordings from the 29 infants who became SIDS victims showed prolonged apnea (>20 sec). Four of the so-called tissue markers of hypoxia and hypoxemia,¹⁰ originally proposed as morphologic confirmation of the apnea hypothesis, were not confirmed in later studies.¹¹

The concepts discussed in the preceding section sug-

gest that while the abnormal breathing patterns observed in the infants suffering a near miss may explain why the near miss episode occurred, they may not necessarily represent evidence that the same patterns occur in the majority of the actual SIDS victims. These and other considerations have recently led Valdes-Dapena, recognized as an unbiased authority on SIDS, to write: "we are now experiencing a counterwave of skepticism concerning the validity of the apnea hypothesis."¹¹ Along the same lines, the Task Force on Prolonged Infantile Apnea of the American Academy of Pediatrics has recently stated: "The vast majority of infants with prolonged apnea are not victims of SIDS; most SIDS victims were never observed to have had prolonged apnea prior to the terminal event" and "... a causal relationship between prolonged apnea and SIDS has not been established. . . ."¹³

Although a biased observer might be tempted to say that the respiratory theory has already suffered several "near miss" episodes and is now "at risk," in all fairness this is not actually the case. Besides the potential significance of the more recent respiratory hypotheses, including those attributing SIDS to surfactant abnormalities¹⁴ and prolonged expiratory apnea,¹⁵ there is no doubt that the respiratory theory provides a valid mechanism for some cases of SIDS and that a breathing abnormality may contribute to SIDS.

What remains to be assessed is the percentage of SIDS cases that can be ascribed to a primary respiratory death; in 1987 this percentage seems smaller than what was thought in the late seventies.

The cardiac theory

Background. As detailed elsewhere,¹ the cardiac theory had its origin in the late sixties. In 1966 Fraser and Froggatt¹ suggested that genetically determined disorders of cardiac conduction might have been involved in SIDS and in 1968 James¹⁶ postulated that lethal arrhythmias or conduction disturbances, largely due to developmental changes in critical areas of the conduction system, might be the final common pathway in SIDS. However, these findings have been seriously challenged by several authors.^{1, 9} In 1973 Froggatt and James,¹⁷ in an important and brilliantly expounded article, examined the possibility that SIDS victims die because of a lethal arrhythmia produced by failure or disturbance in the normal electrical activity of the heart. Their conclusion was that the cardiac hypothesis is *no less likely* than others in which SIDS is ascribed to respiratory causes.

In 1976 I proposed that in some cases of SIDS, developmental abnormalities in the cardiac sympathetic innervation may favor the onset of lethal arrhyth-

mias and may also become manifest before any symptom, thus allowing early identification of some of the babies at risk.² These concepts are based in part on the understanding of the pathogenetic mechanisms of the idiopathic long QT syndrome — the most intriguing example of neurally mediated noncoronary sudden death occurring in apparently healthy individuals with a negative postmortem examination.¹⁸

The hypothesis of cardiac conduction disorders. Periodically, articles appear reporting on the presence or on the absence of abnormalities in the cardiac conduction system of the SIDS victims. These findings are often used⁹ to draw inferences concerning the occurrence of arrhythmic death in SIDS. These studies have significant limitations. The presence, for instance, of accessory pathways (which is viewed as one of the most important findings) only suggests a potential mechanism. A postmortem study cannot reveal if that accessory pathway was functionally active and there can be no evidence that an arrhythmia dependent on preexcitation was the cause of death. The lack of adequate numbers of controls (infants dead from known causes) limits the meaning of these findings. However, the most serious criticism of these studies and of their interpretations is the converse aspect that absence of abnormalities in the conduction system does not at all militate against sudden cardiac death. Indeed, if ventricular fibrillation is the cause of death, no diagnostic abnormalities might be found at autopsy.

The hypothesis of sympathetic imbalance. A hypothesis relating some developmental aspects of cardiac innervation to sudden death during infancy was presented in 1976.² Subsequently, one of its aspects was taken to represent the entire hypothesis, which became known as the “QT” hypothesis.

The origin of this hypothesis is in the proposed pathogenetic mechanisms of the long QT syndrome¹⁸ and in the observed close relationship between the autonomic nervous system and sudden death.¹⁹ Basically, it was proposed that *some* SIDS deaths might result from ventricular fibrillation induced by a sudden increase in sympathetic activity affecting a heart with reduced electrical stability. The specific mechanism proposed was an imbalance between right and left cardiac sympathetic nerves resulting in a left-sided dominance. This type of imbalance is quite arrhythmogenic,²⁰ facilitates ventricular fibrillation, and often manifests itself in prolongation of the QT interval, which is associated with a particularly high risk of sudden death under a variety of circumstances.

How can such an imbalance occur in infants? It is of course possible that some SIDS victims may simply

represent instances of the idiopathic long QT syndrome. This possibility is unlikely to account for more than a few cases. Nonetheless, it has been almost only in this restricted way that this hypothesis has been discussed in the literature. Two other possibilities are more interesting.

The distribution of right and left cardiac sympathetic nerves is likely to be symmetrical and homogeneous in most infants; however, this distribution will probably follow the Gaussian or normal curve, as do most biological phenomena. This implies that a few infants will have to be at the extremes of the curve. Those with the lowest right cardiac sympathetic activity would be the infants at the greatest risk for life-threatening arrhythmias and sudden death. They are likely to show a constant or paroxysmal prolongation of the QT interval.

The sympathetic innervation of the heart becomes functionally complete by approximately the sixth month of life. The right and left sympathetic neural pathways may occasionally develop at different rates, according again to the normal distribution. In this case, a delay in the right side or an acceleration in the left may lead to a *temporary* imbalance of the harmful type described above. A sudden increase in sympathetic activity, elicited by whatever cause (rapid eye movement sleep, exposure to cold, a sudden noise, apnea leading to a chemoreceptive reflex, and so on) may trigger ventricular tachyarrhythmias in these electrically unstable hearts and precipitate sudden death. The possibility of a *time-limited* imbalance in the cardiac sympathetic innervation implies that these infants would be at high risk for SIDS, but only for a limited period of time. Therefore, if they survive the high-risk period, they may have a completely normal life.

The markers of this imbalance (QT prolongation, heart rate abnormalities) may allow the early identification of some future SIDS victims if the sympathetic imbalance hypothesis is correct. The practical implications are self-evident. Since these infants would be at risk of dying because of a sympathetic discharge, effective protection could be conferred by administration of a β -adrenergic-blocking agent for an 8 to 9 month period.

The sympathetic imbalance hypothesis represents one specific aspect of a wider concept, that which implies a critical role, *in a fraction of the cases of SIDS*, for developmental abnormalities in cardiac innervation that would reduce the electrical stability of the heart and predispose some infants to ventricular fibrillation. For example, an insufficient or delayed development of the vagal efferent activity and resultant

lack of its protective effects²¹ may accentuate the arrhythmogenic potential of increases in sympathetic activity. The markers of this sympathetic-parasympathetic imbalance would be a higher than normal heart rate, reduced beat-to-beat variability, or an impaired baroreflex sensitivity.²¹

The value of a scientific hypothesis is in stimulating research in new directions to allow confirmation or rejection. The only way to test the sympathetic imbalance hypothesis is through a large prospective study in an unselected population of infants with the objective of analyzing the QT interval and the heart rate in the neonatal period and then to follow all of these infants for the possible occurrence of SIDS.

The Milan Prospective Study. Beginning at the end of 1975, electrocardiograms were obtained in unselected newborns on the fourth day and during the second, fourth, and sixth months of life. As of October 1986, 13,278 infants have been enrolled and the 1 year survival data are available for 8000 infants. There have been nine SIDS victims and four non-SIDS deaths. Two significant findings have already emerged.

The QT interval corrected for heart rate (QTc) increases from 397 ± 18 (mean \pm 1SD) to 409 ± 15 msec ($p < .0001$), to decline progressively with time, so that by the sixth month it has returned to the same level recorded at birth.²² While all the four non-SIDS victims had a QTc well within the normal limits, six of nine of the SIDS victims had a markedly prolonged QTc (i.e., that exceeding the mean by over 2SD). Four SIDS victims actually had a QTc exceeding the mean by more than 3 SDs.²³

What inferences can be drawn from this ongoing study? The difference in the QTc at the fourth day and the second month of life is important not because of the absolute values, but because it indicates a trend within which a number of individuals (3.6%) have marked QTc prolongations (>40 msec). This study demonstrates conclusively that the QT interval lengthens physiologically and temporarily during the first few months of life. Thus, there is a tendency, which in some infants may become excessive, toward a reduction in cardiac electrical stability at the same time when there is the peak incidence of SIDS. While more data on SIDS victims are needed, these results suggest that an unknown percentage (probably not less than 25%) of infants who subsequently become SIDS victims can be expected to have, on the fourth day of life, a prolonged QT interval.

Given the number of infants with a markedly prolonged QTc (18/1000), our data suggest that the risk of SIDS for these infants would be approximately 40 in

1000 live births. If these findings were confirmed, this would become the single most important risk factor for SIDS.

A multicenter study will begin in 1987 to enlarge the data base of the Milan prospective study. By 1990 approximately 50,000 infants will be studied and the examination of the electrocardiograms of the SIDS victims should provide a definitive answer on the significance of QT prolongation in the first week of life.

The QT controversy. The sympathetic imbalance hypothesis has rapidly generated an unresolved controversy, which was analyzed in detail elsewhere.^{1, 8} Here only a few major points will be outlined, with some comments on the more recently published studies.

First, this hypothesis has often been misinterpreted as equating SIDS to the long QT syndrome, resulting in a considerable confusion. Second, the attempt to verify this hypothesis in the so-called high-risk groups without recognition of the severe limitations listed above has resulted in a number of unjustified conclusions. A few studies of small size²⁴⁻²⁶ have excluded any significant role for QT prolongation in SIDS. This type of report also suffers limitations. For example, Montague et al.²⁶ investigated 17 infants identified as "at risk for SIDS" because of unexplained apnea ($n = 11$) or because they were subsequent siblings of SIDS victims ($n = 5$) or near miss infants ($n = 1$). The QT interval was, if anything, shorter in this group compared with that in 17 control infants. Given the low incidence of SIDS in this group, one would need five to six times more infants (approximately 90 to 100) to have a chance to have one future SIDS victim in that group. It should be clear that a negative finding in a small group of infants with an average risk of 1% (99% false positive) is of no value in answering any hypothesis.

Two studies by Southall et al. are more relevant. In the first¹² the QT interval was measured from Holter recordings. This makes data analysis difficult because the frequency response of the amplifiers of the tape recorder tends to artifactually lengthen the apparent QT interval, which may obscure interindividual differences; nonetheless some of the longest QTc did belong to SIDS victims. To overcome this limitation, a new study²⁷ was performed with standard electrocardiography in 7254 infants, 15 of whom subsequently died of SIDS. The authors conclude that no differences between the SIDS victims and control infants could be identified. Nonetheless, six of the 15 victims had a QTc greater than 440 msec and equal to or greater than the 90th percentile (four times more than expected), and the risk for SIDS of the infants with a QTc in the

upper 90th percentile was 8.3 in 1000, six times greater than that (1.4/1000) of the infants with a QTc below the upper 90th percentile. It is always interesting to see how the same results can be differently interpreted. However, the major limitation of this study is represented by the fact that most recordings were performed on either the first or the second day of life. The variability of the QT interval is extreme during the first 2 days of life, with 16% to 20% of infants showing a very marked prolongation, while by the fourth day this excessive prolongation is evident in only 1.5%. Thus, during the first 2 days one may find a number of "spurious" prolonged QT intervals that will soon disappear. With such a high "noise" level the correct identification of those few infants with a truly nontransient long QT interval becomes difficult. This is why in the Milan prospective study all recordings are obtained on the fourth day of life.

In another recent study on sleep apnea the QT of eight SIDS victims was retrospectively analyzed and was similar to that of other infants.²⁸ It is critical to note that this study was performed while the infants were kept at a room temperature of 90° F. Heating modifies the sympathetic tone and may revert to normal a neurally mediated QT prolongation.

These comments stress the need for a carefully and *specifically* designed protocol to evaluate the sympathetic imbalance hypothesis. In some of these studies,^{27, 28} another problem derives from the use of a huge (>30 msec) standard deviation of the QTc, about twice the usually measured variance (15 to 18 msec). The authors would therefore consider as normal infants with QTcs up to 460 to 470 msec. These values are difficult to reconcile with the generally accepted upper limit of normal of 440 to 450 msec.

The small, but definite and unavoidable subjectivity in the measurement of the QT interval raises the question of bias in both directions, and undeniably contributes to the controversy. This is even more important given the fact that clinically important QT prolongations may be rather small in absolute value, as exemplified by the many concordant studies in patients with myocardial infarction in whom small QT prolongations significantly increase the risk for sudden death.²⁹ The rather definitive statement, "There is no possibility that the long QT, developmental or genetic, or even arrhythmias, can be a major cause of SIDS"³⁰ was perhaps premature.

In conclusion, after the many epidemiologic and pathologic studies, the last decade is witnessing the first large prospective studies designed to test specific mechanisms proposed for SIDS. The respiratory and

the cardiac mechanisms are not mutually exclusive and seem to be the largest contributors to the whole of SIDS, even if their respective importance still remains to be quantified. It would be logical to concentrate the research efforts on answering this question before investigating extensively other less likely possibilities.

The concepts and data presented here indicate that the sympathetic imbalance hypothesis, although not yet proven, has gained plausibility on the basis of current knowledge. The potential for early identification of some future SIDS victims and the likelihood, if the hypothesis is correct, of developing an effective and safe preventive strategy makes even more necessary an accurate and unbiased evaluation of the cardiac hypothesis.

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