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## **Abnormal Respiratory Control Found in Infants Who Later Died of SIDS**

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Some infants who later succumb to sudden infant death syndrome, or SIDS, exhibit impairment in their ability to control breathing during sleep as early as the first week of life, according to a new study funded by the National Institute of Child Health and Human Development (NICHD). These findings differ from earlier reports of normal overall breathing patterns in SIDS victims, and indicate that the defect underlying SIDS may occur before birth, during fetal development.

In this new study, scientists at the University of California at Los Angeles (UCLA), in collaboration with scientists at the Brompton Hospital and the University of Sheffield in Great Britain, recorded heart and breathing patterns in 6,914 apparently normal, healthy infants that ranged in age from two to 65 days. Sixteen of the infants in this group later died of SIDS.

Investigators then compared 16 physiologic recordings of SIDS victims to 35 recordings of age-matched control infants. Unlike previous studies that used gross measures of respiratory rate--and found no differences in overall respiratory rate or variation--this study used a unique measure, originally designed to detect changes in heart rate, to plot the amount of time from one breath to the next, or the breath-to-breath interval.

Using this approach, the investigators were able to compare each breath-to-breath interval, to the previous one while controlling for breathing rate. They found that infants who later died of SIDS exhibited less variation in breath-to-breath intervals at slow breathing rates during sleep than did infants who survived. Specifically, breaths following long breaths showed less change in infants who later died. This finding indicates a more "rigid" control of respiration, and, theoretically, less responsiveness to physiologic input than that found in control infants.

"If you look at the moment-to-moment changes, what you find is that at very slow breathing rates, such as those found during sleep, infants that later die don't change their breathing intervals as much as normal infants," explained NICHD grantee and project investigator Dr. Ronald Harper, of UCLA. "The altered breathing patterns suggest a subtle difference in the control of breathing in infants who die of SIDS. Such a difference points to the brain areas which fail when vulnerable infants encounter a potentially lethal respiratory challenge during sleep." Harper's research team included Drs. V.L. Schechtman and M.Y. Lee of UCLA, Dr. A. J. Wilson of the University of Sheffield, and Dr. D. Southall, formerly of the Brompton Hospital and now at Staffordshire Hospital, who provided the data for the study.

SIDS is defined as the sudden, unexplained death of an infant less than one year of age. Death is associated with a sleep period. Approximately 5,000-6,000 U.S. infants die of SIDS each year, making it the leading cause of death among infants one month to one year of age. Usually, infants are apparently healthy before succumbing to SIDS, and show no signs of danger.

Previous studies by Dr. Harper and colleagues have identified abnormal heart-rate variability in infants who later died of SIDS. These studies found an apparent restriction in the extent of change from one heartbeat to the next in these infants. Because heart and breathing rates are so deeply intertwined--simply changing from a seated to an upright position causes a change in breathing rate and a compensatory change in blood pressure--Dr. Harper and his teams of researchers were

inspired to investigate moment-to-moment breathing patterns. "The cardiac patterning differences indicated that there must be some change in breathing, because heart rate and breathing are so closely interrelated; you can't really get a change in one without getting a change in the other, in normal circumstances," Dr. Harper said. Another factor implicating respiratory-control problems was that SIDS infants have fewer breathing pauses, or apnea, than other infants. Although breathing pauses normally occur in infants, earlier studies done by these researchers found that infants who later died of SIDS exhibited fewer short pauses in breathing, even though their respiratory rates and variability were normal.

The findings from this new study offer the hope of eventually developing screening tests to identify infants who are at risk. The next step is to try to identify the brain structures involved and the developmental stage at which the defect may occur. Dr. Harper and his team are already trying to do this in animal studies using tiny cameras that record the firing of nerve cells in response to various physiological changes, such as an elevation in blood pressure or a change in inspired carbon dioxide. Another promising, but more expensive, approach involves using the technique of functional magnetic resonance imaging to visualize the brain areas that respond to respiratory challenges.

The disturbed breathing signs appear as early as the first week of life, suggesting that factors responsible for the defect operate before birth. "If we know where those brain structures are and if we know when in fetal life those neurons are developing, then we can perhaps target a time during fetal development that an aberration has occurred," explained Dr. Harper, who presented the new study last week in San Diego, Ca., at a press conference held by the Society for Neuroscience.

Other studies, both in this country and abroad, have linked infant prone (stomach) sleeping with an increased risk of SIDS, and back or side sleeping with a reduction in risk. Since 1992, when the American Academy of Pediatrics recommended that infants be placed on their backs or sides to sleep to reduce the incidence of SIDS, the United States has seen a steady decrease in the prevalence of infant prone sleeping. This decrease has been bolstered by the national "Back to Sleep" campaign, launched last year by a coalition of Federal agencies, including the NICHD, and by the American Academy of Pediatrics, the SIDS Alliance, and the Association of SIDS Program Professionals, to disseminate the message to parents and caretakers that back or side sleeping reduces the risk of SIDS.

Already, there are signs that the campaign may be working. A national telephone survey, made last spring, of 1,000 night-time caretakers of infants seven months and younger indicated that infant sleeping practice has changed from 70 percent of infants being placed on their stomach (prone) to sleep, to 70 percent being placed on their back or side, NICHD Director Dr. Duane Alexander announced on October 17 at a Congressional briefing on SIDS. "Although it is too soon to tell for sure, there are encouraging signs that SIDS deaths are declining, especially in states that have active Back to Sleep' promotional campaigns," he said. "Preliminary SIDS rates this past winter were substantially and significantly below those of the previous three years." While these are encouraging signs, Dr. Alexander emphasized that much remains to be done. The goal is to get more than 90 percent of infants to be placed to sleep on their back or side.

The NICHD is distributing free "Back to Sleep" publications and other materials on reducing the risk of SIDS, including a brochure for parents; a simplified-language brochure in both English and Spanish; a brochure for health-care professionals; crib stickers; take-home cards to distribute in hospitals and maternity clinics; posters; videotapes; and public service announcements (for the

media only). To order, write to NICHD/Back to Sleep, 31 Center Drive, MSC 2425, Room 2A32, Bethesda, MD 20892-2425, or call toll-free 1-800-505-CRIB.

The NICHD is part of the National Institutes of Health, the biomedical research arm of the Federal government. Since its inception in 1962, the NICHD has become a world leader in promoting research on development before and after birth; maternal, child, and family health; medical rehabilitation; and reproductive biology, including fertility regulation, and population issues.

At 09:30 AM 3/11/2003 +0000, you wrote:

Good morning Dr. Harper, I was wondering if you could forward me a copy of your research on respiratory control and SIDS? I founded a non profit foundation dealing with choanal atresia and was wondering if there may be a connection. We sure are getting a lot of letters from moms' who have a child born with this birth defect and not diagnosed. Any comments you may have on the matter would be appreciated. Thank you for your time. Jim Loomis Children's Choanal Atresia Foundation [www.babynose.org](http://www.babynose.org)

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Dear Mr. Loomis:

Thank you for the email. It is indeed possible that some cases of SIDS may indeed be cases of unrecognized choanal atresia. It is likely that such an obstruction would be noticed at autopsy, but, as you know, some SIDS deaths are not followed by an autopsy. It is disconcerting that choanal atresia, on occasion, goes unrecognized; even if unilateral; a mild cold can result in near-total occlusion of the nasal passages. A portion of SIDS deaths we believe, result from an inability to restore blood pressure from a period of hypotension. That failure may result from damage/poor development of cerebellar-related structures. (The rationale for that statement is outlined in some of the papers that will be sent to you). One source of the "damage" may derive from a hypoxic episode as a consequence of obstructed breathing, and one source of such obstruction might be choanal atresia. (The relevant cerebellar structures are very sensitive to hypoxia, and are easily damaged).

Thus, we are concerned about choanal atresia, not just from the perspective that the condition may directly lead to asphyxia, but also from the view that the condition may result in less-obviously apparent damage that later results in potential failure during sleep.

I appreciate your pointing me to your web page. We are sending some relevant reprints this evening.

Very best regards,  
Ron Harper