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CURRENT TOPIC

The autonomic nervous system—a role in sudden infant death syndrome

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The sudden infant death syndrome (SIDS) is the major cause of infant mortality in developed countries and remains unexplained.[1 2] While much research related to SIDS over the past 20 years has been into respiratory control, the sleep apnoea hypothesis, this has failed to identify a causal link between poor respiratory control and SIDS.[3 4] The autonomic nervous system is the overall controlling system regulating many of the rescue responses necessary to preserve integrity in a variety of potentially life threatening situations. Given the importance of a functioning autonomic nervous system for survival, and the 'inappropriateness' of most SIDS deaths[1 2] there has been little systematic study of how best to assess autonomic function in infants.

Adelson in 1961 postulated a lethal vagocardiac reflex as a cause of death in SIDS[5] and Fraser and Frogatt suggested a cardiac arrythmia associated with a prolonged Q-T interval.[6] However, a large prospective study failed to show any difference in Q-T interval length between infants with SIDS and controls.[7] Salk *et al* proposed a link between autonomic dysfunction and SIDS[8] as did Schwartz *et al* who suggested that abnormal development of the sympathetic innervation of the heart might lead to ventricular fibrillation and death.[9 10] Southall in a large prospective study found infants who had a future sudden infant death to have more sinus tachycardia and a higher heart rate than controls.[11] Kelly *et al* found these infants to have a higher mean heart rate and more frequent episodes of bradycardia than controls.[4] Additional autonomic effects include profuse watery salivary gland secretions and increased sweat production—both reported associations with SIDS.[1 2 12 13] A group of infants who had sustained an acute life threatening episode (ALTE) have been reported to have exaggerated oculocardiac induced (vagally mediated) cardiac asystoles.[14]

SIDS infants have also been shown to have a lower number of small myelinated vagal nerve fibres, suggesting abnormal or delayed development,[15] in addition to gliosis in the brain stem area controlling vagal function.[16] Carotid bodies from SIDS infants have been shown to contain increased concentrations of dopamine and noradrenaline[17] further suggesting an abnormality in the cathecholaminergic autonomic system. The finding that 84% (21 of 25) of SIDS infants had a significant increase in pulmonary neuroendocrine cell numbers compared with control infants may imply a failure of autonomically mediated discharge of intracellular granules[18] (neuroendocrine cell abnormalities are frequently seen in adults with autonomic neuropathy). Studies examining the intrinsic cardiac conduction system have produced conflicting results perhaps reflecting the difficulty in obtaining suitable control specimens for SIDS infants inherent in any postmortem study.[19 20]

Many SIDS infants are said to have a mild respiratory tract infection,[1 21] diagnosed by a history of snuffles or of being 'chesty' in association with the presence of lung inflammatory cell infiltrates at necropsy, and the roles of nasal obstruction and respiratory infection in SIDS have been debated for years. Most SIDS infants have no other evidence of an acute infection and nasal mucosal thickness and mucus production are under autonomic control. Recently 22 of 50 infants with snuffles, compared with four of 50 control infants, were shown to have postural hypotension raising the possibility that in some infants snuffles may be due to a disturbance in vasomotor tone rather than infection.[22] The intra-alveolar and peribronchiolar inflammatory cell infiltrates found in SIDS[23] are the probable local source of the increased IgA and IgM antibody concentrations reported in lung lavage fluid in SIDS infants.[24] Barrett (in 1954) speculated that these cells might represent a continued 'mild irritation' rather than an acute infection or inflammation and did not feel that they represented an adequate cause of death.[23] Local airway irritant responses are neuropeptide mediated (neurogenic inflammation) by the autonomic nervous system,[25 26] causing enhanced vascular permeability and inflammatory cell (mononuclear, lymphocytic, and polymorphonuclear) chemotaxis. Substance P is the most abundant lung mucosal neuropeptide identified to date and has been shown to stimulate activated human lymphocytic production of IgA and IgM.[27 28] It is known that laryngeal and upper airway 'irritant' receptors can trigger neurogenic inflammation in the upper and lower respiratory tract.[29]

While the role of gastro-oesophageal reflux in SIDS is still debated there is no doubt that reflux of even small quantities of acid gastric contents could stimulate laryngeal and upper airway irritant receptors[30] as could parental smoking—a risk factor for SIDS.[31] Consequently it is possible that the neuropeptide mediated irritant response may, once triggered, be

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exacerbated or continued by concomitant autonomic dysfunction. The abnormal vagal nerve fibres described in SIDS infants are most probably those involved in these responses.[15]

Investigation of autonomic function

Given the likely importance of a normally functioning autonomic nervous system in any 'stressful' situation, including illness, there is relatively little published work relating to autonomic function testing in children. Investigation of autonomic function in children was originally confined to the oculocardiac reflex and the heart rate response to an abdominal air stream stimulus.[32] More recently there has been measurement of heart rate variability, although most studies failed to take account of known confounding factors such as sleep state, percentage of awake time during the recording, the effects of a recent feed, and the ambient temperature.[4 33–35] Investigation of blood pressure responses was limited because of cuff size and difficulties with technique until the development of blood pressure measurement by Doppler and oscillometric methods.

In adults autonomic function testing is largely confined to cardiovascular responses (heart rate and blood pressure) to a wide variety of manoeuvres some of which are detailed below. Any abnormalities detected are thought to reflect widespread autonomic dysfunction including the non-cardiovascular autonomic nervous system.[36–38] Parasympathetic function is investigated by means of the heart rate beat to beat variability and the heart rate response to the Valsalva manoeuvre, deep breathing (expiration:inspiration ratio), and to standing, which is measured as the ratio of the longest R-R interval (called R-R max and generally the 30th beat after standing in adults) to the shortest R-R interval (R-R min or the 15th beat after standing in adults) and called either the 30:15 or the R-R max:min ratio. Sympathetic function is assessed by the blood pressure response to sustained hand grip and the blood pressure response to a change from the supine to the upright position. In adults autonomic dysfunction is graded in degrees of severity and there is an association between increasing dysfunction and sudden, unexpected and unexplained death.[37 38]

Using the heart rate long term beat to beat variability in quiet sleep and the heart rate and blood pressure responses to postural change we have recently shown that autonomic dysfunction is an uncommon occurrence (0–6%) in a group of healthy 11 week old infants.[39] Using the same technique autonomic dysfunction was present in 12·5% of infants where a sibling had died from a SIDS and 46% of infants suffering a well defined severe ALTE. By decreasing the ambient air temperature from 25°C to 20°C the percentage of the near miss group in this study shown to have autonomic dysfunction rose from 46% to 77%. In addition one infant in the near miss group died 14 hours after autonomic function testing showed him to have autonomic dysfunction as shown by a decreased heart rate variability (mean (SD) long term variability 10·3 (6·5), 21 control infants mean (SD) 21·5 (3·3) beats/minute) and a posturally induced fall of 14% in resting blood pressure associated with a progressive bradycardia. A detailed postmortem examination failed to demonstrate a cause of death and showed an increased number of pulmonary neuroendocrine cells and gliosis in the area of the brain stem controlling autonomic/vagal function (postmortem results courtesy of Dr J Gillan).[16]

Recent work in adults has re-emphasised the importance of the autonomic nervous system in the genesis of malignant ventricular arrythmias.[40] As the majority of sudden cardiac deaths in adults occur in people with coronary artery disease most of the published work relates to acute myocardial ischaemia and the period after infarction and sudden death.[41] In this group poor autonomic function, as demonstrated by a reduced heart rate variability, has been shown to be a very powerful predictor of life threatening arrythmic events and sudden, frequently unpredicted, deaths. A recent *Lancet* editorial comments that 'the evidence linking post infarction autonomic dysfunction to arrythmic propensity is now overwhelming'.[42] In adults the combination of hypoxia, secondary to coronary artery disease, and autonomic dysfunction is felt to be the setting in which both combine to produce a lethal arrythmia. Infants with autonomic dysfunction may similarily be arrythmogenic and at increased risk of cardiac arrythmias perhaps requiring an additional stimulus such as hypoxia for their occurrence. The most likely causes of hypoxia in well infants would include sleep apnoea, loss of upper airway control, and ventilation-perfusion mismatching in the lungs. Sleep apnoea has been extensively studied as previously mentioned, although the effect of excess bedding and fever on respiratory and autonomic function need further study.

Upper airway resistance during expiration, by providing an expiratory brake, generates a positive airway pressure and is important in maintaining an adequate functioning lung volume.[43–45] Lung volume in adults has been shown to increase with increasing oronasal airway resistance associated with partial nasal occlusion and to decrease with the drop in resistance associated with mouth breathing that occurs with total nasal obstruction.[43] The nasal airway provides up to 50% of upper airway resistance in infants.[46] In lambs the loss of the normal expiratory airway pressure caused irregular breathing, hypoxia, and hypercapnia especially when the metabolic demand was low.[47] The active expiratory response, described by Hering and Breuer, is directly related to the magnitude of lung inflation when the vagi are intact.[48] Infants, with a pliable chest and decreased muscle tone especially in rapid eye movement sleep, could most economically maintain lung volume by controlling expiratory resistance and duration.[49]

An upper airway resistance that is too low could interfere with lung volume maintenance which is integral to many aspects of lung function. Excessive upper airway resistance would increase the required inspiratory pressure with the consequent risk of pharyngeal

closure during inspiration and consequent hypoxia.[1 50 51]

The autonomic system controls ventilation-perfusion matching in the lungs via both central and local reflex mechanisms that are inter-dependant. The local control of ventilation-perfusion matching is thought to involve the pulmonary neuroendocrine cell system—shown to be frequently abnormal in SIDS.[18] Severe arterial hypoxaemia secondary to intrapulmonary shunting and ventilation-perfusion mismatching has already been proposed as the cause of sudden unexpected death in a group of infants presenting with cyanotic episodes.[52] Infants suffering an acute life threatening episode have been shown frequently to have autonomic dysfunction,[39] and the occurrence of hypoxia would increase any arrythmogenic potential in this group.

Infants with autonomic dysfunction may be at risk from sudden unexpected deaths by simply not being as well equipped to deal with a variety of life threatening situations and succumb where infants with an optimally functioning autonomic nervous system would survive—for example, by failure of the hypoxic arousal response. Alternatively infants with autonomic dysfunction may, like adults, be more arrythmogenic and any additional factor which further increases this tendency, such as hypoxia, could result in a lethal arrythmia. At present there is an urgent need to establish the best method for assessing autonomic function in infants and its subsequent role, if any, in SIDS.

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