Archives Italiennes de Biologie, 139: 185-194, 2001.

AUTONOMIC CONTROL DURING SLEEP AND RISK FOR SUDDEN DEATH IN INFANCY

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INTRODUCTION

In his extraordinary description of sleep physiology in *Sleep and Wakefulness* (21), Kleitman recognized the importance of body position and control of the autonomic nervous system during sleep for maintaining homeostasis, even in the developing infant, and devoted considerable attention to a methodical description of these issues. A remarkable aspect of recent knowledge of circumstances surrounding the Sudden Infant Death Syndrome (SIDS) is the realization that avoidance of certain body positions during sleep, especially the prone position, can reduce the incidence of SIDS by nearly half (10, 41), an astonishing risk reduction considering the simplicity of the intervention. The substantial influence of body position during sleep on the potential for fatal outcome in SIDS suggests that other, as-yet-not-recognized, disorders also may be influenced by comparable position adjustments; disorders of a cardiovascular nature and adult sleep-disordered breathing may be particularly susceptible.

MECHANISMS

The means by which such a seemingly-trivial aspect of sleep behavior as body position can exert such a profound outcome on infant survival are now becoming apparent. The physiological basis for this understanding derives heavily from work of pioneering individuals, some of whom were contemporaries of Dr. Kleitman. The principal insights came with the determination that body position contributes significantly to autonomic and breathing control, that sleep states exert substantial influences on cardiovascular and breathing patterns, and that body position interacts with sleep states to modify cardiorespiratory regulation.

Some of the influences of body position on breathing and blood pressure control relate to simple issues of gravity-imposed redistribution of tissue mass, requiring differential breathing movements and redistribution of vascular pools. However, a major influence derives from vestibular adjustments. Body and head position alter vestibular input, mediated principally from otolith and other transducers through cerebellar reflexes (51). Major output from these reflex actions activates the somatic musculature, including the respiratory musculature, to compensate for postural adjustment and modification of thoracic pressure, a necessary component

for maintaining body position. Significant output from cerebellar coordinating mechanisms also passes to ventral medullary areas, and then to the intermediolateral sympathetic column of the spinal cord.

Vestibular/cerebellar influences on breathing and blood pressure have long been known; paleocerebellar influences on cardiovascular and breathing mechanisms were initially described by Moruzzi (31), and vestibular contributions were later outlined by Pompeiano, Morrison, and colleagues (30, 39, 40). Significant positional aspects have been outlined (8, 51). The cerebellar influences on blood pressure are so substantial that their absence can be life-threatening (25). Vestibular/cerebellar contributions to cardiovascular control frequently operate in a "feed-forward" or anticipatory manner, as demonstrated by head tilt studies in animals (8, 51). Tilt tests now comprise routine components of clinical autonomic evaluation; rapid rising from a supine to vertical position in orthostatic hypotensive patients results in dizziness and frequent fainting from the resulting drop in blood pressure. Appropriate cardiovascular correction for such movements requires blood pressure adjustments acting far too quickly for baroreceptor regulation, and thus likely incorporates vestibular/cerebellar mechanisms. The vestibular/cerebellar mechanisms include sensory information from the position-sensitive otolith receptors and afferent traffic from the inferior olive to the cerebellum, which then projects to reticular and rostral ventrolateral medullary sympathetic areas *via* vestibular nuclei (51). Although aspects of blood pressure regulation by cerebellar mechanisms have been more extensively studied than aspects of breathing, cerebellar regions can modify breathing with hypercapnia (49), and influence phrenic output on stimulation (48), suggesting the potential for significant influences on breathing as well.

However, vestibular/cerebellar contributions are usually overlooked in current views of breathing and blood pressure control, which focus heavily on medullary pacemakers, gasping centers, and brainstem reflex organization of breathing. Peripheral and brainstem chemoreceptor, chest wall inflation, and airflow receptors constitute a major aspect of the breathing control focus, and carotid and aortic baroreceptor action remain the principal issues addressed in modulation of phasic blood pressure control. Cerebellar functions are typically relegated to somatomotor coordination issues, and, more recently, cognitive behavioral aspects. The primary clinical tests for cerebellar damage, for example, include motor coordination function tests, such as finger pointing; such examinations rarely include assessment of blood pressure regulation. Alterations in vestibular/cerebellar contributions to breathing and blood pressure control may significantly enhance the risk for failure in sleep-related pathologies, such as SIDS.

The evidence for cerebellar and vestibular contributions to breathing and cardiovascular control derives from stimulation, macro and single cell recording, lesion, clinical pathology, and functional magnetic resonance imaging studies. The pioneering studies of Moruzzi (31) revealed autonomic alterations induced by stimulation of cerebellar regions and respiratory control aspects from adjacent areas. Morrison and Pompeiano (30) proposed an essential role for vestibular nuclei in mediating phasic components of heart rate and pupillary control during rapid eye

movement (REM) sleep; lesions of vestibular nuclei abolished the REM-related parasympathetic and sympathetic variation (but not phasic ponto-geniculo-occipital activity). The extent of vestibular contributions to blood pressure variation during different states is still being examined; the rapid eye movements during that state may be generated by other than vestibular mechanisms (37), and the nearby pedunculopontine tegmentum is also important for phasic events during the REM state (46).

Physiological Circumstances Associated with SIDS.

The hypothesis that SIDS results from a failure of blood pressure or breathing compensatory mechanisms mediated by vestibular/cerebellar structures derives from several sources. SIDS has classically been viewed as primarily a disorder of breathing, and both obstructed and central breathing failure have been proposed. Most investigators believe that the disorder is sleep-related, since SIDS deaths predominantly occur during sleep. Recent evidence from infants who succumb while being monitored for breathing and heart rate (28), and evidence from hospitalized infants (22) suggest that, at least in some cases, the fatal event is associated with an initiating profound bradycardia and loss of blood pressure while breathing movements are maintained; these events are sometimes associated with profuse sweating, indicating prior sympathoexcitation. The failure sequence appears to be that of a sympathoexcitation followed by a sympathoinhibition and active parasympathetic excitation (enhanced vagal outflow to slow the heart). The events associated with some SIDS deaths thus suggest a primarily cardiovascular, rather than breathing failure. The cardiovascular failure events in SIDS bear remarkable similarities to the sequence of physiological characteristics associated with shock accompanying deep pain or loss of blood, *i.e.*, an initial sympathoexcitation in an effort to sustain blood pressure, followed by a second stage of sympathoinhibition and parasympathetic activation with profound blood pressure loss and bradycardia (15).

Although some SIDS-like fatalities appear to be associated with a shock-like scenario, *e.g.*, fatal events associated with botulism poisoning, other events appear not to accompany deep pain, substantial blood loss, or anaphylactic shock. SIDS does bear a temporal relationship to sleep, and the REM state is associated with significant spontaneous momentary declines in blood pressure; normally these spontaneous declines are rapidly restored by compensatory mechanisms. Cardiovascular failure, particularly of a sympathetic outflow nature, seldom occurs in the absence of compensatory somatomotor "respiratory" or other motor events; the respiratory and cardiovascular systems are integrated to a remarkable extent. Increases in blood pressure are associated with marked apnea (47), while blood pressure declines result in accentuated breathing (34). Hypovolemia, of a degree that induces shock, results in profound respiratory efforts, ranging from tachypnea to repeated large inspiratory efforts, as well as marked extensor muscle activation in intact cats attempting to recover from the blood pressure loss (17; Figure 1).

Of all interactions between blood pressure control and breathing compensatory mechanisms, the exaggerated respiratory and somatomotor events associated with

hypovolemia in normal animals show the potential for cerebellar control reflexes to maintain vital functions. Blood pressure loss apparently results in an "error" signal that triggers cerebellar/vestibular mechanisms to recruit respiratory and other somatic musculature to compensate and recover from the cardiovascular challenge. A major issue in the study of SIDS is determination of why compensatory breathing or somatomotor efforts are not initiated or are ineffective in restoring blood pressure, and why defects in these mechanisms are a concern during sleep, but not during waking states.

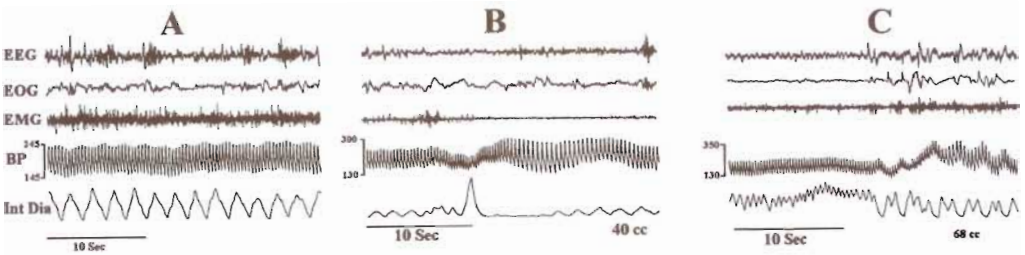

Fig. 1. - *Polygraph traces of diaphragmatic activity (Int Dia) and blood pressure (BP), together with nuchal EMG, eye movement (EOG) and electroencephalographic activity (EEG) during baseline (A), and during hypovolemia with 40 cc blood loss (B) and 68 cc blood loss (C).*

Tachycardia and tachypnea ensued during initial blood withdrawal (**B** and **C**), while isolated (**B**) and sustained (**C**) enhanced respiratory efforts were characteristic of momentary phasic events that accompanied transient elevation of blood pressure from an overall decline. Enhanced skeletal muscle tone (**C**) frequently accompanied the switch to repetitive enhanced respiratory efforts. From Ref. 17.

Structural components.

Lower brain structures associated with control of blood pressure include the ventral medullary surface (VMS), neurons within the midline raphe, and the locus coeruleus; all of these structures show activity declines during REM sleep (29, 42, 44, 45), unlike most neural areas which show greatly enhanced cellular discharge during the REM state (38). The ventral medullary surface plays a particularly significant role in both breathing and cardiovascular control, since lesion, cooling, and chemical and electrical stimulation result in profound effects on breathing and blood pressure control (11, 14, 23, 24). The loss in spontaneous activity of the VMS during REM sleep is particularly remarkable as shown in Figure 2, and occurs across several species (42, 44).

Cerebellar structures do not act in isolation to execute error correction or compensatory breathing and blood pressure responses. The output arm for blood pressure modification from fastigial cerebellar and vestibular nuclei to reticular and ventral medullary areas, and from there to the spinal cord sympathetic column has been well described (51), and input pathways from tilt receptors are also well known. The VMS is strategically localized to act on carotid baroreceptor input that senses changes in blood pressure, since it receives afferents *via* the nucleus of the solitary tract (NTS). The VMS shows extraordinary enhanced responses to losses

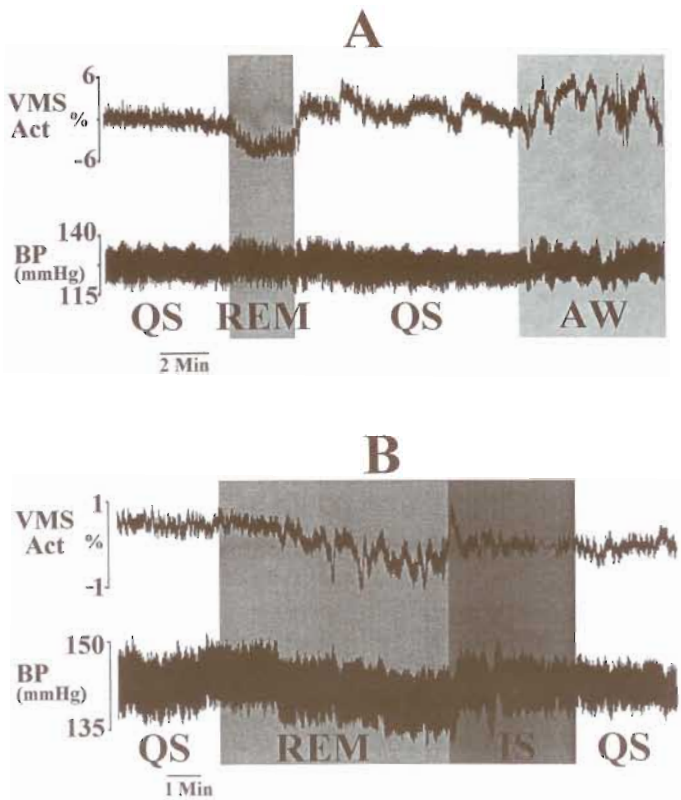

Fig. 2. - **A.** *Representative example from one cat demonstrating decreased activity on the ventral medullary surface (VMS Act) during rapid eye movement (REM) sleep over quiet sleep (QS) and waking (AW). Blood pressure (BP) shows slight elevation during REM in this case.*

B. *A second example of VMS activity decline from the transition of QS to REM sleep in another cat.* From Ref. 17.

in blood pressure during the REM sleep state. Moreover, greatly enhanced "spontaneous" variability in blood pressure occurs during REM sleep. However, despite the greater "responsiveness" of VMS activity to a depressor challenge, a very large body of evidence indicates that forebrain stimulation that normally results in blood pressure or breathing changes are virtually ineffective during the REM state (12, 26); a comparable loss of rostral influences on respiratory rate is found following thermal stimulation of the anterior hypothalamus during REM sleep (32, 36). The loss of effectiveness of more-rostral influences, together with the apparent "undampened" VMS responses to blood pressure challenges, suggest a release of influences from forebrain structures on brainstem areas during that state. The loss of regulatory or dampening influences from rostral sites, combined with an absence of spontaneous activity in the VMS present conditions that contain an element of risk during blood pressure challenges. If the VMS plays an essential

role in blood pressure regulation, and spontaneous activity is lost during REM sleep, together with regulatory influences from the forebrain, any defect in VMS function might place the individual at risk specifically during REM sleep, a risk that might be undetectable during waking with the presence of alternate descending forebrain influences. As noted later, the VMS of SIDS victims, as well as other elements of the cerebellar reflex pathway, are indeed deficient (6, 19, 20, 35). The loss of potential vestibular contributions to phasic autonomic control during REM sleep (30) suggest a process for failure; phasic variation may be responsible for recovery of VMS activity toward normal levels during extreme blood pressure challenges (43). We speculate that damage in the cerebellar/vestibular pathway may result in loss of this potentially compensatory recovery mechanism in REM sleep.

Elements within the cerebellar/vestibular system that play a significant role in modifying cardiovascular and breathing control include the fastigial nucleus, which provides a principal path structure regulating sympathetic outflow. Bilateral lesions of the fastigial nucleus result in a failure to compensate to a hemorrhage (4) or endotoxin shock (25) challenge, with the preparation succumbing to extreme hypotension. Stimulation of the fastigial nucleus modifies phrenic nerve output (48), and neurons in that cerebellar area respond to CO_2 (50). The fastigial nucleus activates prominently to cold pressor or Valsalva challenges in humans (16). It is of interest that both the Lutherer shock data and findings from Moruzzi a half-century earlier emphasize that cerebellar stimulation, either of the vermal paleocerebellum or the fastigial nucleus, exerts influences on extremes of cardiovascular and breathing challenges, and shows little effect on regulation of normal blood pressure and respiratory patterns. Thus, brainstem regulatory mechanisms may mediate "routine" blood pressure and breathing control, while profound changes in blood pressure or exaggerated apnea may require an error correction role for cerebellar structures.

Clinical and pathological evidence.

If experimental animal evidence shows such remarkable vital function effects from interventions to vestibular/cerebellar pathways, then clinical pathology or "experiments of nature" should provide insights into such roles. Indeed, evidence exists that stimulation or damage to cerebellar regions, or to afferent structures projecting to the cerebellum, results in significant cardiovascular and breathing disorders, including obstructive sleep apnea. A variety of cerebellar developmental disorders lead to respiratory consequences in infants (27); other reports describe breathing disturbances in adults following surgical intervention for cerebellar pathology (1,13) or cardiovascular effects following midline stimulation (9). Children afflicted with Congenital Central Hypoventilation Syndrome ("Ondine's Curse") show abnormal functional magnetic resonance image responses in the cerebellar fastigial nucleus to ventilatory challenges (18). The neuropathologic evidence for SIDS includes both immature cerebellar cortex development (7), and gliosis in a principal afferent input to the cerebellum, the inferior olive (6). The inferior olive also shows diminished serotonergic receptor binding in victims of SIDS (20).

Regions within the inferior olive show *c-fos* activation to 5-HT-induced profound hypotension in rats (Bandler, personal communication). Other areas with major roles in blood pressure control, including the raphe obscurus, a structure particularly implicated in hypotensive responses (5), and the arcuate nucleus of the VMS show deficiencies in serotonergic binding, as well as muscarinic and kainate binding in SIDS victims (19, 35). The collective neuropathologic evidence implicates damaged or delayed development in afferent input to cerebellar regions, or in cerebellar cortex in infants with significant breathing or cardiovascular difficulties or who succumb to SIDS, and suggests that some of these deficits include neurotransmitter issues. The conditions which lead to such damage are unclear, but epidemiological evidence of prenatal maternal smoking (2) and low maternal hematocrit findings (3), hint of the occurrence of nicotinic or hypoxic injury in fetal life; Purkinije cells receiving inferior olive projections may be particularly susceptible to damage from such conditions, as they are for other toxic agents (33). The possibility of a hypoxic event damaging structures post-natally also cannot be excluded.

SUMMARY

A variety of clinical pathology and experimental animal evidence suggests that cerebellar and vestibular structures mediate marked challenges to blood pressure and breathing, and are particularly involved in compensatory somatomotor and breathing efforts to overcome substantial losses in blood pressure. At least a subset of victims of the Sudden Infant Death Syndrome (SIDS), a sleep-related disorder, succumbs to a profound bradycardia and hypotension prior to respiratory cessation, suggesting a failure of autonomic control, or incompetent compensation of somatomotor and respiratory efforts, to overcome the cardiovascular collapse. The clinical and neurotransmitter evidence from SIDS victims implicates afferent and efferent components within vestibular/cerebellar blood pressure control systems in SIDS victims. Experimental evidence from animals suggests vestibular and cerebellar structures exercise critical roles in mediating autonomic responses to body position and extreme changes in blood pressure. The position-dependent risk for SIDS, together with the neuropathological evidence, suggests a significant role for vestibular/cerebellar structures in mediating the fatal outcome for the syndrome.

Acknowledgements. - Supported by RO1-HL-22418, RO1-HD-22506, RO1-HD-22695, and RO3-HD-36228.

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