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AROUSAL RESPONSE TO RESPIRATORY EVENTS IN PREMATURE NEWBORNS

by

Helen L. Dulock

DISSERTATION

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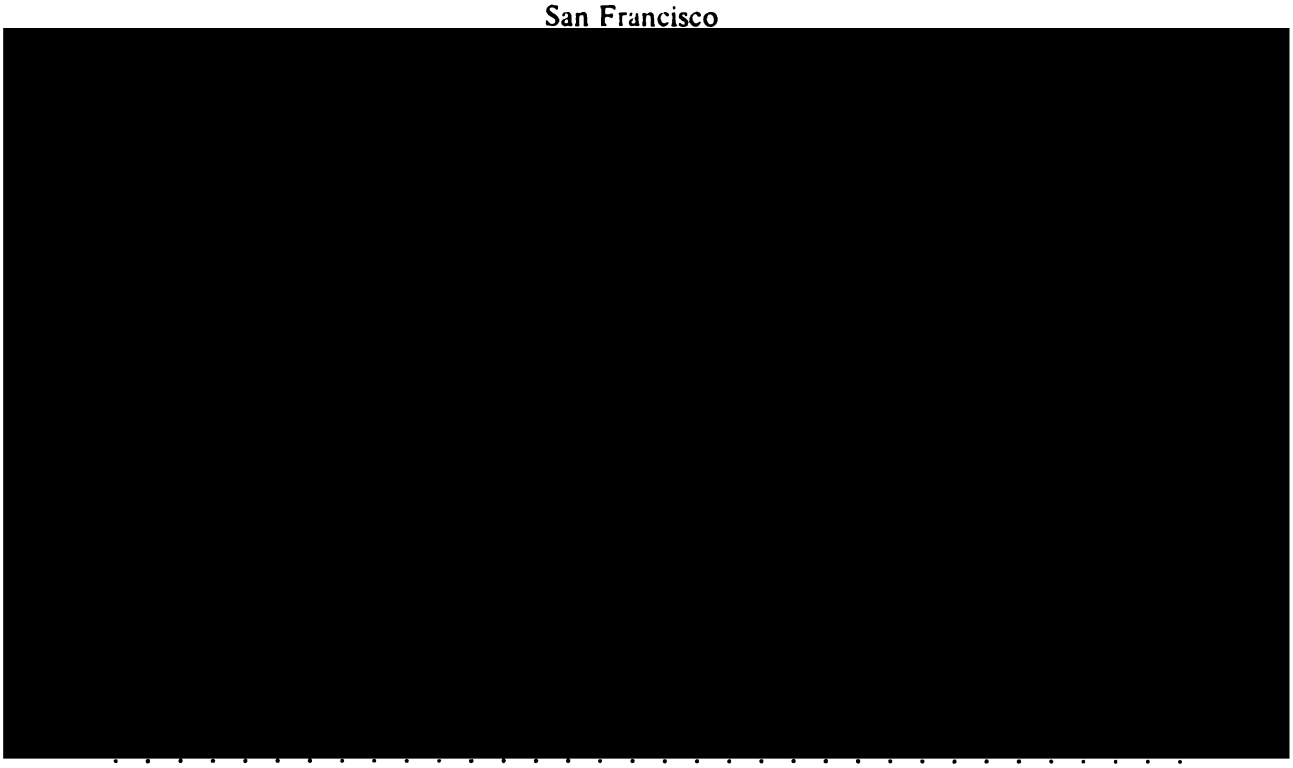

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June 1989

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AROUSAL RESPONSE TO RESPIRATORY EVENTS
IN PREMATURE NEWBORNS

Helen L. Dulock

ABSTRACT

The ability to arouse from sleep in response to respiratory events such as apnea, hypoxia, and hypercarbia is an important protective mechanism.

The following hypotheses were investigated: 1) apnea in prematures is terminated by arousal; 2) the frequency of arousals, both spontaneous and in relation to hypoxic and hypercarbic challenges will increase with postnatal age; 3) arousal will occur at a higher oxygen saturation with advancing postnatal age, and 4) arousal will occur at a lower carbon dioxide level with advancing postnatal age.

Subjects were 11 prematures with a mean gestational age at birth of 30 weeks, studied initially at a mean postnatal age of 7 weeks and again at 14.5 weeks. During sleep the following variables were recorded: heart rate, respiratory rate, oxygen saturation, skin surface oxygen and carbon dioxide, respired carbon dioxide, esophageal pressure and sleep states by behavioral criteria. Data were collected during baseline sleep while breathing room air, 17% oxygen and 2, 4, and 6% carbon dioxide.

Of 34 recorded apneic episodes 14 were interrupted by behavioral arousal. This may be evidence of maturation and integration of the reticular activating system and respiratory center.

Congruent with the above were findings that behavioral arousal at the later compared to the early postnatal age was: 1) significantly decreased during baseline sleep; 2) decreased in response to breathing 17% oxygen and 2, 4, and 6% carbon dioxide, and 3) significantly increased in REM versus NREM sleep at both postnatal ages.

In response to 17% oxygen arousal threshold was lower (i.e., mean oxygen saturation was higher) at the later postnatal age for both arousers and nonarousers, but was statistically significant by postnatal age only for the total group. Fewer subjects aroused to 17% oxygen at the later postnatal age, and mean oxygen saturation was higher at the later postnatal age, whether at arousal or at the end of 17% oxygen. In response to increased inspired carbon dioxide there was no significant difference in arousal threshold (i.e. transcutaneous carbon dioxide tension) by postnatal age or by arousal status. Fewer subjects aroused to increased inspired carbon dioxide at the later postnatal age.

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CHAPTER I

INTRODUCTION

Statement of the Problem

The ability to arouse from sleep in response to respiratory stimuli such as hypoxemia or hypercarbia is an important protective mechanism because: (a) arousal to the awake state allows appropriate conscious behavior to occur; (b) arousal may result in the acquisition of reflexes which are state dependent; and (c) arousal results in a reflex increase in neural drive to all respiratory muscles (Phillipson & Sullivan, 1978). Thus arousal is a potent respiratory stimulus. In fact, the voluntary excitation of breathing during wakefulness has been termed the "wakefulness stimulus" to ventilation (Fink, 1961).

Phillipson and Sullivan (1978) were the first to suggest that while the study of ventilatory responses to respiratory stimuli is important, the arousal response to these same stimuli is an important but forgotten variable. Responses to respiratory stimuli, are more relevant to clinical disorders of hypoventilation or apnea during sleep, than, for example, tactile, acoustic or other kinds of stimuli.

As referred to in sleep physiology, arousal is a stimulation or excitation of the reticular activating system (RAS). Hypoxemia and hypercarbia can occur as a result of disturbance in respiratory function and both are known to stimulate not only breathing, but also the RAS and produce cortical arousal (Hugelin, Bonvallet, & Dell, 1959). The response to stimulation varies in intensity and may produce a complete

awakening from sleep or simply a change in the level of operation of the autonomic nervous system through stimulation of the RAS (Guilleminault, 1982). During sleep in adults the arousal response leads to electroencephalogram (EEG), cardiac and respiratory changes. However, the EEG changes are not necessarily those of awakening, but may consist of a change from Stage III or IV nonrapid eye movement sleep (NREM) to Stage I or II NREM or to rapid eye movement (REM) sleep.

The physiological recognition of arousal involves a broad range of descriptions. Experimentally, arousal may be defined by a variety of methods, including: (a) frank behavioral awakening with the assumption of purposeful, conscious behavior; (b) a change in the stages of sleep as defined by EEG criteria; and (c) a transient desynchronization of the EEG (Bowes, 1984). Although arousal can refer to a spectrum of electrophysiological events, it should not be assumed that identical mechanisms are responsible for each level of this spectrum (Bowes, 1984).

The role of arousal as a protective mechanism has been demonstrated in several studies of adults with obstructive sleep apnea syndromes (OSAS). Researchers have found an almost invariable association between apnea termination and an arousal response, which was then followed by restoration of upper airway patency and a resumption of air flow (Kurtz & Krieger, 1978; Guilleminault, Tilkiani, & Dement, 1976; Remmers, de Groot, Sauerland, & Anch, 1978; Orr, 1980). It is assumed that the arousal response is causally related to apnea termination, although not all apneas are terminated by arousals.

Arousal from sleep may also play a role in preventing physiological accidents during sleep. For example, Sullivan, Kozar, Murphy, & Phillipson (1979) demonstrated that stimulation of the trachea with

water during sleep results in a protective reflex consisting of arousal from sleep, coughing and clearance of the water from the trachea. However, the cough reflex was not elicited unless preceded by an arousal from sleep, and these reflex mechanisms were shown to be significantly depressed during REM sleep. Coughing appeared to be coupled to arousal, such that a stimulus sufficient to produce coughing during wakefulness did not produce coughing in the absence of arousal from sleep. Thus, arousal may produce a fundamental change in the nature of the ventilatory response to a respiratory stimulus. In addition, apnea and bradycardia, which are known reflex responses to laryngeal stimulation occurred only during sleep.

Factors that influence the arousal response from sleep have not been well studied. Sleep fragmentation is one variable that has been shown in animal data to impair arousability in response to hypoxia (Bowes, Woolf, Sullivan, & Phillipson, 1980). Steinschneider (1972) proposed a possible relationship between apnea occurring during sleep in infants and sudden infant death syndrome (SIDS). Guntheroth (1983) has hypothesized that the crucial area of abnormal physiology in SIDS is impaired arousability after apnea. An impaired or depressed arousal response is thought to explain better the possible roles of the many risk factors for SIDS (Navelet, Payan, Guilhaume, & Benoit, 1984). In a comparative study of normal infants and those who had previously experienced an apparent life threatening event (ALTE), arousal in response to a hypoxic challenge was achieved in only 9% of the ALTE subjects compared to arousal of 70% of the normal subjects (McCulloch, Brouillette, Guzzetta & Hunt, 1982). There was no significant difference between the groups in the number arousing to a hypercarbic

challenge; however, the carbon dioxide level at which arousal occurred was significantly higher ($p<.05$) in the group who had experienced an ALTE. Similar findings have been reported by others (van der Hal, Sargent, Platzker, & Keens, 1982). More recently, Fewell and Baker (1987) demonstrated in an animal model that, if the rate of change of oxygen desaturation is great enough during active sleep, electrocortical signs of hypoxia and primary apnea may actually precede arousal from sleep.

The ontogeny of arousal responses is largely unknown (Bowes, 1984). Arousal thresholds are thought to vary in different species during early life, with higher levels of stimulation required to elicit arousal in early postnatal life (Bowes, 1984). The fetus responds to hypoxemia by decreasing or inhibiting fetal breathing movements; however, there is no arousal response. This absence of an arousal response suggests that in the fetus the threshold for arousal is very high (Walker, 1986); yet it is known that the carotid chemoreceptors are active in utero (Blanco, Dawes, Hanson, & McCooke, 1982). A higher arousal threshold in early life could be viewed as teleologically advantageous because both REM and NREM sleep are thought to be vital to growth and maturation (Horne, 1979).

The arousal response has not been extensively studied in premature newborns. Premature newborns are a vulnerable population in relation to arousal response to respiratory stimuli because factors influencing respiratory control are undergoing adaptation and maturation. Apnea is a common occurrence in prematures and is the most common form of respiratory control derangement in the neonatal period (Rigatto & Brady, 1972a). Short apneas are often still present in premature infants at the time of hospital discharge (Hageman, Holmes, Suchy, & Hunt, 1988).

Secondly, premature newborns have been identified by epidemiological criteria as being at increased risk of SIDS (Peterson, 1966; Steel & Langworth, 1966; Valdes-Dapena, 1967; Bergman, Ray, Pomeroy, Wahl, & Beckwith, 1972; Naeye 1977); yet little is known about the characteristics of premature infants who are likely to be affected. Infants born prematurely are estimated to account for 18% of all SIDS deaths (National Institutes of Health Consensus Development Conference, 1986). Several studies have indicated that factors predisposing an infant to sudden death have their origin in the prenatal or perinatal period and may involve a subtle disturbance of cardiorespiratory control mechanisms (Harper, 1983; Naeye, Ladis, & Drage 1976; Stebbens, Alexander, & Southhall, 1987; Steinschneider, Weinstein, & Diamond 1982; Valdes-Dapena, 1979).

Thirdly, the arousal threshold is postulated to be higher in early postnatal life (Bowes, 1984; Walker 1986). In addition, in some studies the arousal threshold has been observed to be higher in REM sleep compared to NREM sleep (Phillipson, Sullivan, Read, Murphy, & Kozar, 1978) and premature infants spend 65-80% of total sleep time in REM sleep (Parmelee, Wenner, Akiyama, Schultz, & Stern 1967). During REM sleep in premature newborns, the postural muscles are inhibited (Bryan & Bryan, 1977), the work of breathing is increased (Krill, Andrew, Bryan, & Bryan, 1976), lung volume is decreased (Henderson-Smart & Read, 1979a) and metabolic rate is increased (Strothers & Warner, 1978). Apnea has been observed to be more common during REM compared to NREM sleep in prematures (Gabriel, Albani, & Schulte, 1976; Gabriel, Helmin, & Albani, 1980).

The multiple factors that influence the control of respiration is presented in Figure 1. This diagram indicates the central role of sleep and arousal on respiration. It is not known whether apneic episodes in prematures are interrupted by an arousal response, what the relationship between arousal threshold and ventilatory responses to induced hypoxia and hypercarbia is and whether these responses and thresholds are related to postnatal age.

The following hypotheses are to be investigated:

1) Apnea in prematures is terminated by an arousal response;
2) The frequency of arousal responses, both spontaneous and in response to hypoxic and hypercarbic challenges, will increases with increasing postnatal age;
3) Arousal threshold as indicated by oxygen saturation values will be lower with increasing postnatal age in response to induced hypoxia;
4) Arousal threshold as indicated by transcutaneous carbon dioxide values will be lower with increasing postnatal age in response to induced hypercarbia.

Given the relationships diagrammed in Figure 1, a schematic diagram of the variables to be investigated in this study are presented in Figure 2.

Operational Definitions

Premature infants: Premature infants are defined as those born at less than 34 weeks gestational age. The designation of prematurity will be determined by a standardized gestational age assessment

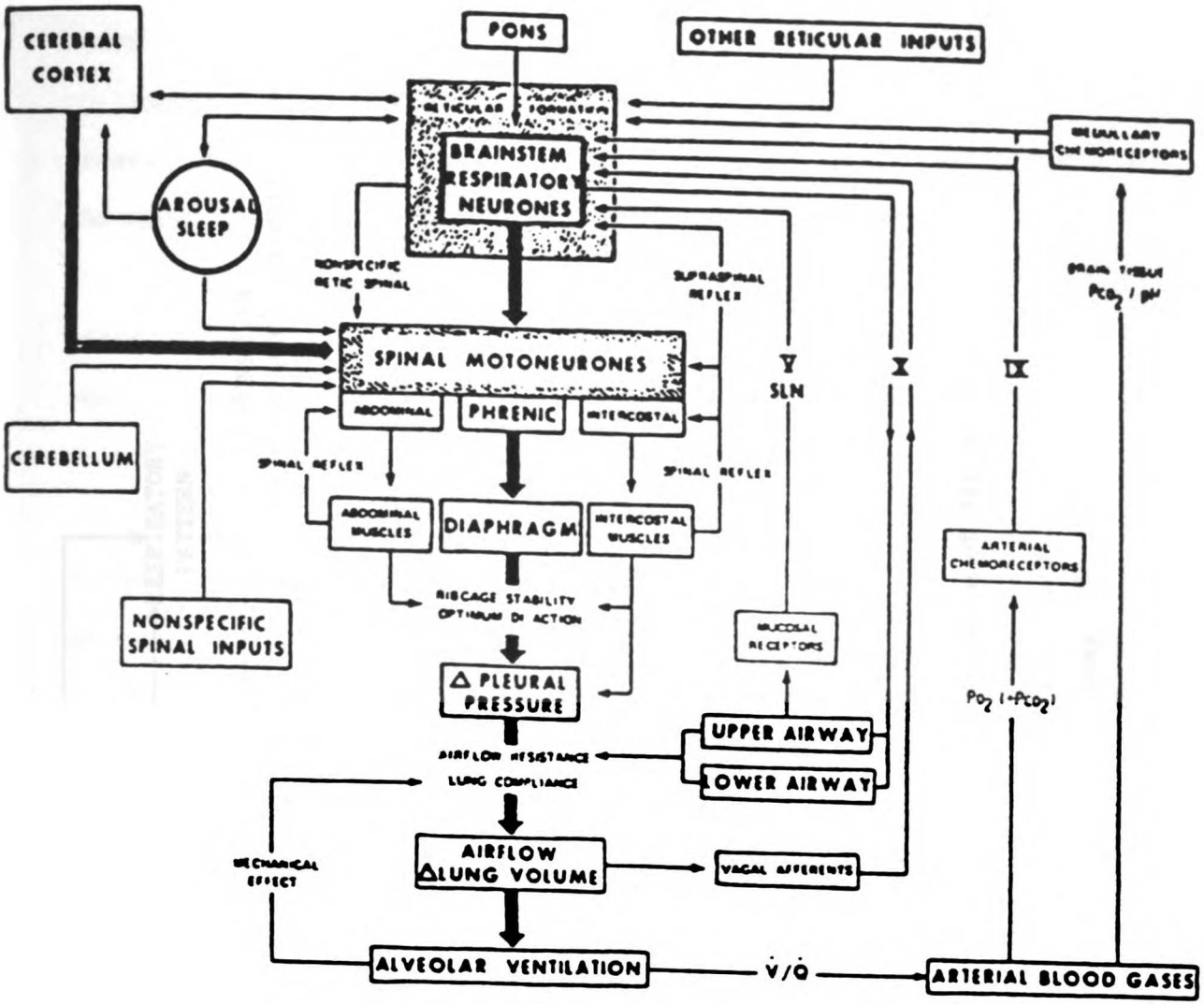
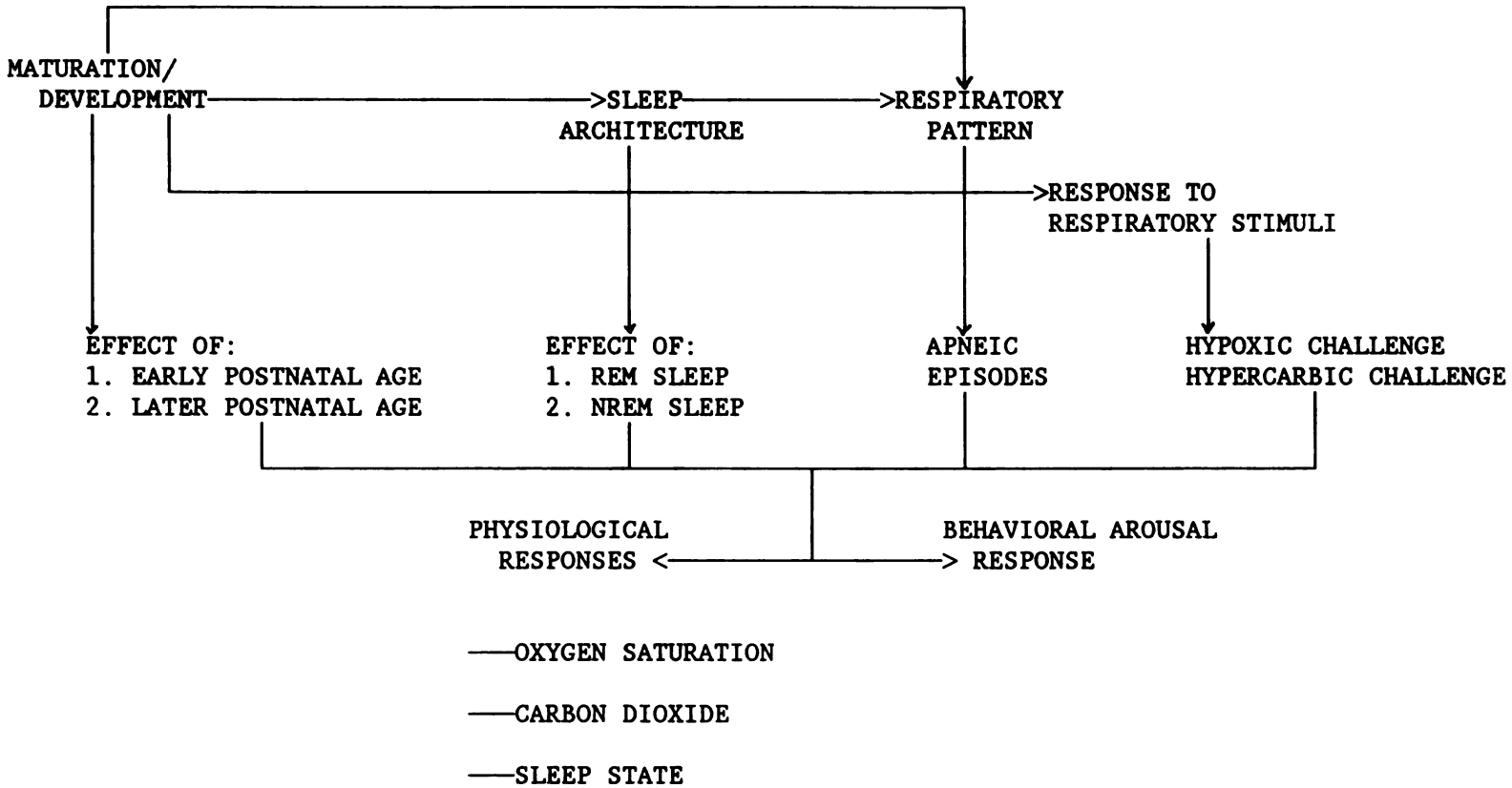


Figure 1. Diagrammatic representation of the respiratory control system. Note central role of arousal/sleep acting at the major sites of integration in the brainstem and spinal cord as well as on the cerebral cortex. Heavy arrows indicate involuntary (from brainstem) and voluntary (from cerebral cortex) afferent pathways. Roman numerals indicate cranial nerves and SLN is the superior laryngeal nerve. V/Q represents the ratio of pulmonary ventilation to pulmonary blood flow.

Reprinted from D. J. Henderson-Smart (1984). Regulation of Breathing in the Perinatal Period. In N. A. Saunders & C. E. Sullivan (Eds.), Sleep and breathing (p. 425), by courtesy of Marcel Dekker, Inc., New York.



Legend:

Horizontal lines: Relationships
Vertical lines: Decreasing level of abstraction of variables

Figure 2. Schematic diagram of major variables of study.

performed by the nursery house staff and documented on the subject's chart.

Apnea: Apnea is the cessation of respiratory effort or airflow for greater than 6 seconds, as documented by strain gauge and recorded on the Grass^{R} polygraph.

Central apnea: Central apnea is the cessation of respiratory effort and of nasal air flow, as measured by strain gauges around the chest and abdomen, and by respired carbon dioxide, respectively. Both will be recorded on the Grass^{R} polygraph.

Obstructive apnea: Obstructive apnea is the cessation of nasal airflow as documented by respired carbon dioxide in the presence of continuing respiratory efforts, as indicated by the chest and abdominal strain gauges and recorded on the Grass^{R} polygraph.

Periodic breathing: A breathing pattern characterized by 3 or more consecutive respiratory pauses lasting 3 seconds or longer, interspersed by less than 20 seconds of regular breathing.

Mixed apnea: Mixed apnea is an episode of central apnea followed by an obstructive apneic episode.

Arousal: Arousal is a transient change in state indicated by generalized body movements. These movements may be associated with changes in skin color, such as mottling or flushing of face; eyes may be closed or intermittent fluttering of eyelids. There is no crying.

Awake: The condition of being awake is indicated by: sustained body movements with sustained eye opening, or by crying.

REM sleep state: REM sleep is indicated by the following: a) rapid eye movements, b) closed eyes, c) phasic body, limb, or facial movements which may be associated with closed eyes.

NREM sleep state: NREM sleep is indicated by: a) absence of rapid eye movements, b) closed eyes, c) startles which may be associated with closed eyes. (startles are sudden contractions of many muscles groups, lasting a few seconds with an immediate return to a relaxed state).

Arousal threshold: Arousal threshold is the oxygen saturation value or the transcutaneous carbon dioxide value at the time of arousal.

Early postnatal age: Early postnatal age, for purposes of this study, will be between 5 and 11 weeks postnatal age.

Later postnatal age: Later postnatal age, for purposes of this study, will be between 12 and 16 weeks postnatal age.

CHAPTER II

THEORETICAL BACKGROUND

Regulation of Respiration in the Perinatal Period

Respiration and its control change in the fetus and newborn during the progression from late gestation, through parturition and into the newborn period. Some of these changes occur rapidly and dramatically, such as the change from episodic breathing movements in the fetus to the continuous breathing pattern in the newborn. Other changes are more subtle and progress over time, such as the response to hypoxia, which inhibits breathing movements in the fetus, produces a transient increase in ventilation, followed by a decrease in the newborn, but produces a sustained increase in ventilation in the adult. This chapter discusses how the major variables of this study influence respiratory regulation and pattern in the premature newborn.

Sleep States and Breathing in the Newborn

In utero, fetal breathing movements (FBM) are normally linked to sleep state, in that FBM's occur only in association with low voltage fast activity on the electrocorticogram (ECG) and with rapid eye movements, both of which are indicative of the active or rapid eye movement (REM) sleep state (Dawes, 1974; Boddy & Dawes, 1975; Ioffe, Jansen, Russell, & Chernick, 1980). In addition, carbon dioxide, which is a respiratory stimulant in postnatal life, stimulates FBM's only

during REM phases of sleep in the fetus (Boddy, Dawes, Fisher, Pinter, & Robinson, 1974). Therefore, either the threshold for initiating FBM is increased with the onset of non-rapid eye movement (NREM) sleep or some inhibitory mechanisms are occurring during this phase of sleep that prevent FBM's from occurring at the same time. Thus, one of the changes that must occur immediately in the transition from fetus to newborn is the maintenance of a regular breathing pattern regardless of sleep state.

The predominant sleep state of the premature and term newborn is REM sleep, accounting in prematures for 65% - 80% of total sleep time (Parmelee, Wenner, Akiyama, Schultz, & Stern, 1967; Gabriel, Albani, & Schulte, 1976). During sleep, breathing is regulated by two distinct but functionally integrated elements, the metabolic control system and the behavioral system. During REM sleep breathing is less responsive to metabolic influences and is more driven by the behavioral component, thus variability in ventilatory pattern and responses are more common. During REM sleep the mean respiratory frequency and mean minute ventilation are increased, with larger breath-to-breath variability compared to NREM sleep (Bolton & Herman, 1974; Finer, Abrams & Taeusch, 1976; Hathorn, 1974). Sleep state also affects the respiratory muscles. The postural muscles are inhibited during REM sleep, and the inhibition of the intercostals affects the mechanics of breathing (Bryan & Bryan, 1977; Hagan, Bryan, Bryan & Gulston, 1976). The rib cage is more unstable during REM sleep, which increases the work of breathing (Knill, Andrew, Bryan & Bryan, 1976). In normal term newborns, lung volume has been shown to be decreased an average of 30% during REM sleep (Henderson-Smart & Read, 1979a). A loss of tonic activity of the

diaphragm during REM sleep in newborns also has been documented (Muller, Gulston, Cade, Whitton, Froese, Bryan, & Bryan, 1979; Prechtl, Van Eykjern, & O'Brien, 1977).

In addition, newborns have a small end expiratory volume causing the lungs' oxygen buffering capacity to be low while their rate of metabolic oxygen consumption is approximately twice that of an adult (representative values are 8 and 4 ml minute per kg, respectively). During REM sleep in prematures, the metabolic rate increases (Strothers & Warner, 1978) and oxygen stores in the lungs are reduced; thus only brief pauses in respiration cause a rapid decrease in arterial oxygenation (Henderson-Smart & Read, 1979a). Apneic episodes in prematures are common and are more often associated with bradycardia during REM sleep than during NREM sleep (Gabriel, Albani, & Schulte, 1976; Gabriel, Helmin, & Albani, 1980; Schulte, Busse, & Eichhorn, 1977). Arterial oxygen values, as indicated by transcutaneous oxygen monitoring, are lower and more variable during REM compared to NREM sleep, in both premature and term newborns (Gabriel, Helmin, & Albani, 1980; Herrell, Martin, Pultusker, Lough, & Fanaroff, 1980; Okken & Rubin, 1979).

Sleep state may also have an impact on the ability to arouse in response to respiratory stimuli. For example, in fetal lambs hypoxemia appears to initiate the arousal response to upper airway obstruction primarily during active (REM) sleep, but not during quiet (NREM) sleep (Baker & Fewell, 1987). Arousal in response to bronchopulmonary stimulation has been shown to be depressed in REM sleep in an adult animal model (Sullivan, Kozar, Murphy, & Phillipson, 1979). These responses have not been studied in early life.

Response to Hypoxia

The ventilatory response to hypoxia is mediated by the peripheral chemoreceptors, primarily those in the carotid bodies. The carotid chemoreceptors are active in the fetus although they respond to much lower arterial oxygen tension than during postnatal live (Dawes, 1984; Blanco, Dawes, Hanson, & McCooke, 1984). Chemoreceptor sensitivity is reset from fetal to adult values during the first few days following birth, and it appears that this re-setting of the carotid chemoreceptors is dependent upon or initiated by the increase in arterial oxygenation that occurs after birth (Blanco, Hanson, & McCooke, 1985). In the lamb, hyperoxia induced by mechanical ventilation of the fetus before birth caused resetting to occur prior to delivery (Blanco, Hanson, McCooke, & Williams, 1987), while in the rat a hypoxic environment in early postnatal life produced a persistence of the immature inhibitory response to hypoxia (Eden & Hanson, 1987).

Chemoreceptor activity is assessed by observing changes in ventilation in response to breathing various concentration of inspired oxygen. The fetal arterial oxygen pressure is normally about 23-25 torr, and acute reduction to 12-15 torr in fetal animals causes decreased and eventual cessation of FBM (Boddy, Dawes, Fisher, Pinter, & Robinson, 1974; Martin, Murata, Ikenoue, & Ettinger, 1975). Dawes, Gardner, Johnston, and Walker (1983) concluded that there is an area in or above the pons which is necessary for the inhibition of breathing during hypoxia in the fetus, and hypoxic inhibition of FBM is not due to a depressive effect on the medulla or to insensitivity of the carotid bodies. The effects of acute hypoxia on the human fetus is not known.

An arousal response to hypoxia is absent in the fetus, but present in the newborn (Walker, 1986). The absence of this response in the fetus suggests that the threshold for the production of arousal is very high in the fetus, especially since the carotid chemoreceptros are active in utero.

The human adult responds to hypoxia with sustained hyperventilation (Dripps & Comroe, 1947). The newborn has a biphasic response with an initial increase followed by a decrease in ventilation (Cross & Oppe, 1952; Brady & Ceruti, 1966; Rigatto, Brady & Verduzco 1975b). A biphasic response to hypoxia also has been observed in newborn rabbits, kittens and monkeys (Schwieler, 1968; Blanco, Hanson, Johnson, & Rigatto, 1981; Woodrum, Standaert, Mayock & Gutherie, 1981), but not in newborn lambs and puppies (Henderson-Smart & Read, 1979b). The initial increase in minute ventilation is the result of an increase in both tidal volume and respiratory frequency, while the subsequent decrease is due primarily to a decrease in respiratory frequency with an increase in respiratory pauses (Rigatto, Brady, Verduzco, 1975b).

The mechanisms responsible for the initial increase in ventilation reflect peripheral chemoreceptor stimulation, and the subsequent ventilatory depression generally has been attributed to the effects of overriding central hypoxic depression (Cross, 1954; Rigatto, Brady, & Verduzco, 1975a,b). However, Hanson (1986) believes the secondary fall in ventilation is not due to direct depression of the respiratory centers by hypoxia because 1) true depression implies hypoventilation, but the decrease in ventilation is usually not accompanied by an increase in arterial carbon dioxide tension and in fact a decrease in carbon dioxide has been observed (Haddad, Gandhi, & Mellins, 1982), and

2) after acute exposure to hypoxia a decrease in ventilation occurs, which if the inspired oxygen is further reduced, will be followed by a stimulation of ventilation and then another reduction in ventilation. The ventilatory depression also may reflect an increase in cerebral blood flow during hypoxemia, which would contribute to a decrease in brain tissue carbon dioxide levels and reduction in the drive to breathe (Henderson-Smart, 1984). Cerebral blood flow increases in acute hypoxia with a time constant of 30 to 40 seconds (Edelman, Santiago, & Neubauer, 1984) which approximates the time of the decrease in ventilation.

In human newborns this biphasic response occurs whether alveolar carbon dioxide is decreased, maintained at normal levels, or increased during hypoxia (Brady & Dunn, 1970). In addition, this biphasic response is independent of gestational age, having been observed in both premature (from 28 weeks gestational age) and term newborns (Rigatto, Brady, & Verduzco, 1975b). However, this response is influenced by postnatal age in that term newborns are have a sustained hyperventilatory response to hypoxia by approximately 10 days of age, and prematures, by approximately 18 days of age.

Several investigators (Haddad & Mellins 1984; Henderson-Smart & Cohen, 1988) make the point that the biphasic response in the newborn may not be unique, only more dramatic, since even adults have a late decrease in ventilation during isocapnic hypoxia, with the decrease not occurring for about 10 minutes. Thus the biphasic response observed in the newborn may be due to a predominance of the central nervous system inhibitory effects of hypoxia as seen in the fetus. The major differences between the newborn and adult response to hypoxia are that 1) the decrease in ventilation occurs much sooner in the newborn than in

the adult, and 2) ventilation decreases to levels below baseline in the newborn, but rarely does so in the adult (Rigatto, 1979; Kagawa, Stafford, Waggener, & Severinghaus, 1982).

The early studies describing the biphasic ventilatory response to hypoxia were not controlled for sleep state. The ventilatory response to 100% and 15% oxygen (0_2) during wakefulness and sleep was examined in 11 prematures (gestational age, 32 weeks; postnatal age, 31+ 5 days) by Rigatto, Kalapesi, Leahy, Durand, MacCallum and Cates (1982). Sleep states were determined based on data from electrocorticograms (ECG), electroocularograms (EOG), and electromyograms (EMG) as described by Gabriel, Albani and Schulte (1976). The administration of 15% 0_2 resulted in an immediate and significant increase in ventilation during wakefulness, REM, and NREM sleep. This was followed by a late (5-minute) decrease in ventilation during wakefulness and REM sleep, but in NREM sleep the initial increase in ventilation was sustained, but not as much as in adults. Further studies are needed in prematures born at various gestational ages and the variables need to be studied longitudinally to confirm, refute or expand upon these observations.

Response to Carbon Dioxide

The central chemoreceptors can be stimulated by either an increase in arterial CO_2 or a decrease in pH of the cerebrospinal fluid surrounding the ventral surface of the medulla at the level of the fourth ventricle. The evaluation of the ventilatory response to inhaled CO_2 may be done either through rebreathing for 6-8 minutes from a bag containing oxygen or, as has been done more recently, by using a steady

state technique in which the subject sequentially breathes increasing concentrations of 2%, 4% or 6% CO_2 for a set number of minutes.

In utero, the fetal arterial carbon dioxide is approximately 10-15 torr higher than the maternal carbon dioxide; however, even this level does not stimulate a continuous pattern of breathing in the fetus (Dawes, Fox, Leduc, Liggins, & Richards, 1972). Inducing hypercapnia in the fetus produces several well established effects: 1) hypercapnia increases both the amount of low voltage electrocortical activity (corresponding to active or REM sleep) and increases the proportion of low voltage activity in which FBM occurs; 2) hypercapnia increases the depth and regularity of FBM (Chapman, Dawes, Rurak, & Wilds, 1980); and 3) hypercapnia does not induce FBM's during quiet or NREM sleep despite arterial carbon dioxide greater than 60 torr (Boddy, Dawes, Fisher, Pinter, & Robinson, 1974). There is no evidence of central nervous system arousal of the unanesthesized fetal lamb in utero in response to hypercapnia (Dawes, Gardner, Johnston, & Walker, 1982).

In the premature and term newborn the administration of up to 2% CO2 produces an increase in ventilation mediated primarily by changes in tidal volume (Cross, Hopper, & Oppe, 1953; Avery, Chernick, Dutton, & Permutt, 1963; Frantz, Adler, Thach, & Taeusch, 1976; Rigatto & Brady, 1972a,b). The sensitivity to CO_2, (the slope of the line describing ventilation versus alveolar carbon dioxide [corrected for body weight]) was found to be similar in term newborns and adults during normoxia (Avery, Chernick, Dutton, & Permutt, 1963; Rigatto & Brady, 1972a,b.). However, the CO_2 response curve in neonates (minute ventilation versus inspired carbon dioxide concentration) is shifted to the left of that of adults by about 4 torr. This has been explained on the basis of a lower

bicarbonate level in neonates (Avery, Chernick, & Dutton, et al. 1963). Further maturation of the CO_2 response also occurs during the first week of life in full-term newborns (Taeusch, Carson, Frantz, & Milic-Emili, 1976). The newborn's response to CO_2 is not affected by immature acid-base responses, as the acid base regulation in cerebrospinal fluid in newborns is similar to that of adults (Krauss, Thibeault, & Auld, 1972).

Premature newborns have a decreased CO_2 sensitivity compared to term newborns (Frantz, Adler, Thach, et al., 1976; Krauss, Klain, Waldman, & Auld, 1975; Rigatto, Brady, & Verduzco 1975b). The slope of the ventilatory response curve in prematures increases by nearly 50% between 32 and 37 weeks gestational age and by about 60% within the first month of postnatal life (Rigatto, Brady, & Verduzco, 1975b). The increase in the slope with postnatal age was independent of gestational age. The mechanism for this increasing response with gestational and postnatal age is not definitively known, but is thought to be centrally mediated and dependent upon a growing maturation of the central nervous system. In an attempt to determine if the decreased response to CO_2 in prematures was due to less sensitive central chemoreceptors or to mechanical inability of the respiratory muscles to generate an appropriate ventilatory response, respiratory output in prematures was compared to that in term infants (Moriette, Chaussain, Radvanyi-Bouvet, Walti, Pajot, & Relier, 1983). Minute integrated diaphragmatic activity (EMG, [diaphragm] times respiratory frequency) was used as an index of central respiratory output, which increased less in response to inhaled CO_2 in prematures than in term newborns. Indices of mechanical effectiveness (minute ventilation divided by mean inspiratory

diaphragmatic activity) were not different, suggesting that the respiratory pump effectively transforms the central output into negative intrapleural pressure or volume. These results indicate that the decreased response is likely to be centrally mediated. Similar conclusions were reached by Frantz, Adler, Thach, et al. (1976) using a different methodology.

Premature newborns with frequent episodes of apnea have been shown to have a significantly reduced ventilatory ratio (VR) slope in response to breathing 0%, 2% and 4% CO2 when compared with those without apnea (Hazinski, Severinghaus, Marin, & Tooley, 1984). The VR is calculated as follows:

$$VR = \frac{P_sCo_2 \text{ (breathing air)}}{P_sCo_2 - P_1Co_2 \text{ (breathing } Co_2 \text{ in air)}}$$

where P_sCo_2 is the skin surface carbon dioxide and P_1Co_2 is the partial pressure of Co_2 in the inspired gas. The VR is then plotted as a function of its corresponding skin surface carbon dioxide tension and a slope calculated by simple linear regression. This slope is similar to a standard ventilatory response slope; the greater the slope of the ventilatory ratio, the greater the subject's ventilatory response to inhaled carbon dioxide. When apneic episodes ceased, the VR slope increased to a range that was not different from the slopes of those without apnea. In the non-apneic subjects, the VR slope significantly increased with postnatal age. In another study, subjects without apnea increased their minute ventilation twice as much as those with apnea, for a similar change in arterial carbon dioxide (Gerhardt & Bancalari, 1984a,b).

Studies of healthy premature and term newborns have demonstrated no differences in the ventilatory response to 3% CO_2 during REM or NREM sleep and administration of CO_2 did not affect sleep state (Davi, Sankaran, MacCallum, Cates, & Rigatto, 1979). Differences during REM and NREM sleep state also were not observed in healthy prematures given low concentrations (0.5-1.5%) of CO_2 to breathe; however, the increase in ventilation in response to CO_2 did differ depending on whether the prior respiratory pattern was periodic or regular (Kalapesi, Duran, Leahy, Cates, MacCallum, & Rigatto, 1981). With periodic breathing, the increase in ventilation was due primarily to an increase in frequency, while with prior regular breathing, this increase was due to an increase in tidal volume. Increases in instantaneous minute ventilation in response to 2% CO_2 were similar in both sleep states in healthy newborns studied during the first 4 months of life (Haddad, Leistner, Epstein, Epstein, Grodin, & Mellins, 1980). These increases were due to increases in tidal volume, a finding that is not in agreement with earlier observations of significantly decreased minute ventilation to 4% CO_2 in REM compared to NREM in prematures studied during the first 24 weeks postnatally (Bryan, Hagan, Gulston & Bryan, 1976). Fagenholtz, O'Connell and Shannon (1976) reported an insignifcant decrease in CO_2 sensitivity during REM sleep in infants 2-3 months of age.

In adults, the ventilatory response to an increase in arterial CO_2 is enhanced if moderate hypoxemia also is present (Lloyd, Jukes, & Cunningham, 1958). In the human newborn, this response is quite the opposite. Even with mild hypoxia, the ventilatory response to CO_2 is depressed. With increased oxygen levels, the ventilatory response to carbon dioxide is increased (Rigatto, Brady, & Verduzco, 1975b). The

influence of oxygen on cerebral blood flow and on brain tissue carbon dioxide could partly explain this response. At low oxygen levels, cerebral blood flow increases, and this could be expected to lower brain tissue carbon dioxide and reduce breathing effort; with increased oxygen levels, cerebral blood flow would be expected to fall and brain tissue carbon dioxide is likely to accumulate, thus increasing the drive to breathe.

The ventilatory response to carbon dioxide also has been studied in otherwise normal infants who have experienced a near miss SIDS episode. During NREM sleep these infants have been shown to hypoventilate and to have a significantly decreased ventilatory response to 5% CO2 (22.2 versus 63.1cc/kg/min/torr) in comparison to a control group of infants (Shannon, Kelly, & O'Connell, 1977). This difference was due primarily to a significantly smaller increase in tidal volume. Three of the 11 near miss SIDS infants in this study subsequently died at home during sleep. Similar ventilatory response findings in infants with near miss SIDS have been reported (Hunt, McCulloch, & Brouillette, 1981); however, other investigators have found the slope of the ventilatory response curve in near miss SIDS to be either normal (Fagenholtz, O'Connell, & Shannon, 1976) or increased (Haddad, Leistner, Lai, & Mellins, 1981). Or, as has been noted, the ventilatory response to carbon dioxide breathing may be only intermittently abnormal (Ariagno, Nagel, & Guilleminault, 1980; Brady, Ariagno, Watts, Goldman, & Dumpit, 1978).

In summary, the control of respiration in newborns differs in many respects from that of the fetus and of the adult. These differences are thought to reflect a period of transition in the development and maturation of the respiratory control system. The premature has a

biphasic ventilatory response to hypoxia initially and changes to a response of sustained ventilation approximately two weeks following birth. An increase in ventilation also occurs in response to increased inspired carbon dioxide. Sleep state is an important modulator of respiration, and the effect of different sleep states during hypoxia and hypercarbia in newborns is an area of continuing investigation. Sleep state may also play an important role in arousal threshold in response to respiratory events. The next chapter addresses the arousal response to various respiratory stimuli in animals, adults, and infants.

CHAPTER III

LITERATURE REVIEW

Studies of arousal responses in relation to various respiratory stimuli are reviewed in this section. These studies represent the current state of knowledge development regarding variables that influence the arousal response to various respiratory stimuli in animals, adults, and infants. A summary table of selected data from these studies is provided at the end of this chapter.

Arousal Studies in Animals

Effect of Sleep Fragmentation

The hypothesis that fragmentation of nocturnal sleep by multiple arousals might result in impaired arousability to respiratory stimuli during periods of apnea was investigated (Bowes, Woolf, Sullivan, & Phillipson, 1980). This is important because obstructive sleep apnea syndrome in adults is characterized by repeated apneas during sleep, many of which are terminated by electrocorticogram (ECG) and behavioral evidence of brief arousal, followed by restoration of airway patency and airflow (Guilleminault, Tilkiani, & Dement, 1976; Remmers, de Groot, Sauerland, & Anch, 1978). The fragmentation of sleep by brief recurrent arousals, rather than sustained sleep deprivation, was the variable of interest. Thus sleep fragmentation was designed to simulate the multiple brief arousals that occur in obstructive sleep apnea syndrome.

The subjects were five dogs who were chronically prepared with a permanent tracheostomy and who were studied before and after 2-3 consecutive nights of sleep fragmentation. Sleep fragmentation was induced by brief (30-second) periods of noise played at regular intervals (every 150 seconds) from a tape recorder activated by a time switch. Each epoch of noise had a mixture of 2 or more of 12 common sounds, (music, telephone ringing, typewriter, etc.) and provided rapid fluctuations in sound tone and intensity, thus avoiding habituation of the arousal response to acoustic stimuli as described by Sharpless and Jasper (1956).

Both control and post-sleep-fragmentation measures were made during the afternoons, when the dogs normally slept for 2-3 hours. The ventilatory and arousal responses to three specific respiratory stimuli were assessed: (a) hyperoxic progressive hypercapnia, (b) isocapnic progressive hypoxia, and (c) chemical stimulation of the larynx with water. Measures were made of end-tidal carbon dioxide (CO_2) concentration by continuous sampling of tracheal gas through an infrared CO_2 analyzer (Beckman LB-2) from which alveolar CO_2 pressure could be calculated. Oxygen saturation was measured by an ear oximeter (Hewlett Packard 47201A). A cuffed endotracheal tube was inserted through the tracheostomy and attached to a pneumotachograph (Fleisch No. 2) and to a differential pressure transducer (Statham PM 5). The airflow signal was integrated electronically to provide tidal volume and calculation of instantaneous minute volume of ventilation.

During studies of the responses to laryngeal stimulation, the cuff of the endotracheal tube was inflated with water and attached to a pressure transducer. Changes in cuff pressure thus reflected changes in

tracheal smooth muscle tone. Rapid eye movement (REM) and non rapid eye movement (NREM) sleep states and wakefulness were determined by ECG and behavioral criteria. The ECG and behavioral activity of the dogs were frequently monitored during the process of sleep fragmentation. More than 80% of the noise epochs produced a brief period of arousal even on the third night of the sleep fragmentation. No criteria or description of arousal was given. The dogs were observed between the epochs of noise, to validate that sleep was re-established.

The effects of sleep fragmentation was obvious from the day-time behavior of the dogs; they demonstrated excessive daytime sleepiness by attempting to nap at every opportunity and were lethargic in their morning exercise activity. These subjective impressions were confirmed by measuring sleep latency after arousal, response to hypercapnia, hypoxia and laryngeal stimulation. Sleep latency was defined as the time from the instant of EEG arousal from slow wave sleep to the return of sleep, defined as at least 15 seconds of synchronized high voltage EEG activity. By these criteria, mean sleep latency times in all of the dogs decreased significantly ($p<.001$) as a result of sleep fragmentation, regardless of the specific stimulus used to produce arousal. There was an overall decrease in mean sleep latency from 2.76 minutes in the control period to 1.62 minutes in the post fragmentation period ($p<.001$). After 4-5 nights of recovery sleep following the fragmentation, sleep latencies returned to control values.

Ventilatory responses to hyperoxic progressive hypercapnia were assessed by a modified re-breathing technique and were not impaired by sleep fragmentation. In contrast, arousal responses to hypercapnia following sleep framgentation were impaired during both NREM and REM

sleep, with a mean increase in alveolar carbon dioxide ($PACO_2$) of 3.4 torr at arousal in both stages of sleep. During REM sleep, the control levels of $PACO_2$ at arousal were higher than in NREM sleep, as had been shown previously by Phillipson, Kozar, Rebuck, & Murphy (1977) and further increases occurred after fragmentation. Thus, arousal responses to hypercapnia in both REM and NREM sleep were impaired as a result of sleep fragmentation.

Ventilatory response to isocapnic progressive hypoxia, as indicated by instantaneous minute volume of ventilation oxygen saturation, showed decreases during both REM and NREM sleep; however, in neither case was the change significant. Arousal responses to isocapnic progressive hypoxia also were impaired in both sleep states, compared to control values, with a decrease in the mean oxygen saturation at the time of arousal of 10% during NREM sleep and over 12% during REM sleep. During NREM sleep the mean oxygen saturation required to arouse the dogs decreased from a control value of 80% to 70% after sleep fragmentation. During REM sleep, the mean arousal oxygen saturation (66%) was lower than NREM sleep during control studies and decreased to less than 55% after sleep fragmentation. In one animal, the arousal response to hypoxia continued to be impaired after one night of normal sleep.

Although the ventilatory responses to hypoxia were unimpaired by sleep fragmentation, arousability from both REM and NREM sleep in response to hypoxia were markedly decreased after sleep fragmentation. Arousal responses to laryngeal stimulation were assessed by instilling small volumes (0.1-1.0 ml) of distilled water onto the larynx. During control conditions, there was an all-or-none response during sleep, such that a stimulus insufficient to produce arousal also failed to induce

coughing or tracheal smooth muscle constriction and a stimulus sufficient to awaken the dog invariably elicited ventilatory and airway responses.

Following sleep fragmentation, the arousal response to laryngeal stimulation was impaired, with significantly larger volumes of water required to elicit arousal. In the absence of arousal, cough and tracheal smooth muscle constriction also generally failed to occur. Since sleep fragmentation did not impair ventilatory responses to hypercapnia or hypoxia, the authors concluded that these findings are consistent with a general hypothesis of impaired arousal as a disturbance of central mechanisms and that the fragmentation process caused functional disturbances somewhere within the reticular activating system or nuclei rostal to the pontomedullary respiratory neurons. The mechanisms by which sleep fragmentation impairs arousal responses to respiratory stimuli were not examined in this study and have not been delineated (Bowes & Phillipson, 1984). However, an increase in arousal threshold to auditory stimuli after sleep deprivation has been shown to involve a central mechanism, rather than a decrement in peripheral sensory organ function (Frederickson & Rechtschaffen, 1978).

Clinically, the results from this study may explain the profound degree of oxygen saturation that often is seen in patients with obstructive sleep apnea syndrome. Impaired arousal responses in these patients, with subsequent decreases in oxygen saturation, may contribute to the pulmonary hypertension and corpulmonale that develops with chronic obstructive sleep apnea syndrome. In the short term, impaired arousability may be an adaptive response to maintain sleep homeostasis; however, in the chronic diseased state, it is clearly a maladaptive process.

In infants with sudden infant death syndrome (SIDS), epidemiologic studies indicate that many infants experienced a mild upper respiratory infection just prior to or at the time of death (Valdes-Dapena, 1977). While the respiratory infection, itself, may not account for the death, it may interfere with normal sleep patterns and result in a degree of sleep fragmentation, which could then contribute to an impairment in arousability. Thus, although the antecedent illness may be resolved, an impaired arousal response may persist for several days following sleep fragmentation. Therefore, an apneic episode occurring during sleep may proceed uninterrupted and produce hypoxic cerebral depression and death.

The effect of sleep fragmentation on the arousal response to upper airway obstruction using auditory stimuli was investigated using newborn lambs (Fewell, 1987). Measurements of oxygen saturation, heart rate, respiratory rate, and blood pressure were made in 6 chronically instrumented and tracheostomized newborn lambs between 8 and 14 days of age. Sleep states were determined by ECG, electrooculargrams (EOG) and nuchal electromyograms (EMG). Sleep fragmentation was produced by 30 seconds of noise, followed by two minutes of quiet for a period of 36-42 hours in duration. Data for analysis consisted of measurements made during a control period during both REM and NREM sleep and during experimental periods of upper airway obstruction following uninterruped sleep and following sleep fragmentation. Sleep fragmentation produced small but statistically significant increases in the time to arousal and decreases in the oxygen saturation at arousal in response to upper airway obstruction during NREM sleep but not during REM sleep.

The author concluded that these changes were small and were of questionable biological significance. Short term sleep fragmentation per

se was felt not to impair significantly the arousal response to respiratory stimuli in newborn lambs. Several points are important in considering these results and their interpretation. First, sleep fragmentation was induced by auditory stimuli; however in this study the stimuli actually produced arousal 83-93% of the time (range) during NREM sleep and only 58-94% of the time (range) during REM sleep. In contrast, Bowes, Woolf, Sullivan et al (1980) in the study reported above, had more than 80% of the noise epochs produce a brief arousal and their animals also experienced longer periods of sleep fragmentation (2-3 consecutive nights versus 36 to 42 hours). Secondly, upper airway obstruction was experimentally produced in the newborn lambs by obstructing the tracheostomy tube with an inflated balloon; airway obstruction by deflation of the balloon was terminated once arousal occurred. Thus, it is unclear to what extent the arousal response was affected not only by sleep fragmentation, but also by the effect of upper airway obstruction.

Tammeling (1972) suggests that increased intra-pulmonary pressures, such as those occurring during obstructive apnea, produce proprioceptive stimulation that contributes to lightening of sleep state. In addition, the differences between these 2 studies may be influenced by the use of different species of different postnatal age (i.e. lambs in the newborn period versus adult dogs). Future studies of inducing sleep fragmentation by auditory stimuli and then assessing the arousal response should report the intensity (decibel level) of the stimulus presented, not just its duration, in addition to careful description of the actual percentage of times arousal was actually produced in response to the auditory stimulus. The temporal relationship between the

auditory stimulus and whether or not it produced arousal should also be described in order to determine if habituation to the stimulus may be occurring. The effects of sleep fragmentation on human newborns have not been investigated.

Effect of Bilateral Carotid Body Denervation and Vagal Blockade on Arousal Response

The arousal response to progressive hypoxia in dogs has been shown to be primarily dependent upon the carotid bodies (Bowes, Townsend, Kozar, Bromley, & Phillipson, 1981b). It should follow then that the arousal response to airway occlusion would be impaired in carotid-deafferented animals. Alternatively, if arousal is dependent upon mechanical stimuli generated in the lungs and airways during occluded respiratory efforts, blockade of the vagus nerves should produce a decrease in the arousal response to airway occlusion.

Accordingly, the independent effects of bilateral carotid body denervation and bilateral blockade of the vagus nerve on the arousal response to airway occlusion during sleep in dogs was studied (Bowes, Townsend, Kozar, Bromley, & Phillipson, 1981a). Four animals were studied under three conditions: 1) in the intact state, 2) following bilateral carotid denervation in two dogs, and 3) following bilateral vagal blockade in two dogs. The dogs were chronically prepared with a tracheostomy; sleep stages and ventilatory measures were as defined in the study described above. In addition, airway occlusion was achieved by closing a three-way valve connected to the endotracheal tube. Airway occlusion was instituted at end expiration and was maintained until the

moment of arousal. The oxygen saturation corresponding to the point of awakening was used as the oxygen saturation at arousal.

After each episode of airway occlusion, steady states of sleep and of ventilation were re-established before subsequent occlusion trials were conducted. Following control studies, two of the dogs underwent bilateral surgical denervation of the carotid bodies using standard surgical procedures. Recovery from the surgery was uneventful, and studies were not resumed until at least one week post operative. The effectiveness of the surgical procedure in denervation of the carotid bodies was indicated by resting alveolar hypoventilation (mean increase in awake alveolar PCO_2 of 11 torr) and by abolition of the ventilatory response to hypoxia. Arousal responses to airway occlusion were examined 1 to 4 weeks after carotid denervation. Following the control studies, the remaining two dogs underwent bilateral blockade of the cervical vagus nerves, which was achieved by cooling the exteriorized vagal loops with copper radiators through which cold alcohol circulated. The effectiveness of this procedure in blocking vagal conduction had been previously established (Phillipson, Murphy, Kozar, & Schultze, 1975). Arousal responses to airway occlusion during vagal blockade were confined to periods of NREM sleep.

In the intact animals, the mean oxygen saturation at arousal from total airway occlusion was not significantly lower in REM sleep compared to NREM sleep (84.9% vs. 88.7%, respectively; (.05 <p>.01). After carotid body denervation arousal responses were greatly delayed, despite prolonged occlusion, during which oxygen saturation decreased to less than 60%. The effects of denervation were so profound that in order to avoid episodes of severe hypoxemia, occlusions were subsequently

terminated whenever arterial oxygen saturation values reached 60% in NREM sleep and 50% in REM sleep. The accuracy of the ear oximetry is uncertain at oxygen saturation values below 50%. Oxygen saturation following bilateral carotid body denervation was significantly lower than values in the intact animal ($p<.005$). If airway occlusion was allowed to continue despite profound decreases in oxygen saturation, arousal, when it did occur, was very slow and lethargic, in contrast to the abrupt and alert arousal response of the intact animal. On several occasions when occlusion was maintained, arousal failed to occur at all, and the dogs required resuscitation with oxygen before regaining consciousness.

Arousal responses following vagal blockade were examined in two animals during NREM sleep. The mean oxygen saturation following vagal blockade was not significantly different from the values obtained in the same animals with intact vagal nerves.

The ventilatory response, following carotid body denervation, to the respiratory load imposed by total airway occlusion was impaired. Although both the intact and denervated animals progressively increased their inspiratory efforts during airway occlusion, the magnitude and rate of increase of end inspiratory pressures were significantly less following carotid body denervation.

During airway occlusion, afferent stimuli are presumably generated from different sources, such as the carotid and aortic chemoreceptors, lung and airway receptors, central chemoreceptors, and respiratory muscle and chest wall receptors. A significant decrement in arousability to airway occlusion was found in this study by elimination of only the carotid chemoreceptors. These same chemoreceptors long have

been known to be the major sensory receptors involved in the ventilatory response to hypoxia and have recently been shown to mediate the arousal response to hypoxia (Bowes, Townsend, Kozar, et al, 1981b).

Thus, it seems reasonable to conclude that hypoxia is the primary stimulus that induces arousal after airway occlusion during sleep and that hypoxia is the primary stimulus responsible for the progressively increasing ventilatory efforts during airway occlusion. Because vagal blockade blocks conduction of afferent stimuli from the aortic chemoreceptors, the present results indicate that the aortic bodies are not substantially involved in the arousal response to either airway occlusion or hypoxia.

It is possible that carotid body denervation decreases arousability in general, since denervation resulted in moderate hypercapnia and mild hypoxemia under resting conditions and both of these conditions can impair central nervous system function. In addition, the elimination of carotid chemoreceptor afferent input may have removed significant tonic input to the reticular activating system. However, the daytime behavior and the afternoon sleep patterns of the dogs were not perceptibly altered after carotid deafferentation. Previous studies have shown that arousal responses to laryngeal stimulation, which are independent of arterial chemoreceptor function, is unaltered by carotid denervation (Bowes, Townsend, Kozar, et al., 1981b). These factors imply that the impaired arousal response to airway occlusion induced by carotid denervation was not merely the result of a generalized decrease in arousability.

Upper airway occlusion during sleep is the predominant pathophysiological feature of the obstructive sleep apnea syndrome;

however, airway occlusion alone may not be sufficient to induce a significant clinical disorder. Concurrent carotid body dysfunction may be one factor that contributes to the clinical picture by impairing arousability to hypoxia during sleep. In SIDS, there is evidence at autopsy of the effects of chronic hypoxia (Naeye, 1974) however this is not a consistent finding in all cases of SIDS. With chronic hypoxia, one would expect hypertrophy of the carotid bodies; however, usually small carotid bodies have been found (Naeye, Fisher, Ryser, Whalen, 1976). There is also conflicting evidence regarding the amount of glomic tissue or the number of neurosecretory glanules in the carotid bodies of infants dying of SIDS (Cole, Lindenberg, & Galioto, 1979; Perrin, Cutz, Becker, & Bryan, 1984). In infants who have died of SIDS, significantly higher concentrations of dopamine and noradrenaline have been found in the carotid bodies, when compared to age matched control infants dying of other known causes (Perrin, Cutz, Becker, Bryan, Madapallimatum, & Sole, 1984). Dopamine is known to decrease frequency and tidal volume of respiration (Olson, Hensley, & Saunders, 1974) may inhibit the response to hypoxia (Nishino, & Lahiri, 1981) and is thought to be important for the arousal mechanisms during a hypoxic event (Bowes, Townsend, Kozar, et al., 1981). Clinical studies of infants with apnea of infancy found no differences in serum dopamine concentrations between those who aroused to a hypoxic challenge and those who did not; however, in those who had an abnormal hypoxic arousal response, both the serum epinephrine and serum norepinephrine concentrations were elevated while awake, during natural sleep and during the hypoxic challenge, compared to those with a normal hypoxic arousal response (Rodriquez, Warburton, & Keens, 1987).

Arousal Responses to Hyperoxic Hypercapnia

The pattern of breathing is more irregular during REM sleep than during NREM sleep in adults, newborns, and in animals (Aserinsky, 1965; Bolton & Herman, 1974; Phillipson, Murphy & Kozar, 1976) however, the mechanisms underlying this irregularity are not well understood. To determine if progressive hypercapnia would abolish the irregular breathing pattern of REM sleep and to document ventilatory responses to hyperoxic hypercapnia, a study of these responses was carried out (Phillipson, Kozar, Rebuck, & Murphy, 1977).

The subjects were three dogs who were chronically prepared with a permanent tracheostomy, with the endotracheal tube attached to a pneumotachygraph (Fleisch No. 2), and the pneumotachygraph attached to a pressure transducer (Statham PM5) for monitoring airflow rates. Tracheal gas was sampled continuously for measurement of CO_2 concentration. The stages of sleep were determined by ECG and behavioral criteria. Hyperoxic hypercapnia was induced by re-breathing from a wedge spirometer containing a gas mixture of 6% to 7% CO_2 and 93% to 94% oxygen (O2). Each rebreathing experiment continued until the dog awoke, which invariably occurred within 5 minutes. Rebreathing experiments during NREM sleep were confined to periods in which the EEG showed predominant slow wave activity comparable to Stage 3 REM sleep in humans. Rebreathing experiments during REM sleep were confined to periods of a typical EEG pattern, REM and twitches of the ears, whiskers, nose or lips. The ECG was monitored visually, and the timing of arousal or of any other change in sleep stage in relation to respiratory events, noted precisely.

The animals were studied during REM and NREM sleep on the same and on different days, since only one rebreathing run could be obtained before the procedure inevitably led to arousal. After a short period of wakefulness, the animals would generally fall asleep again, so that three or four rebreathing runs could be obtained in both REM and NREM sleep by continuing the study through a number of sleep cycles. Attempts were made to alternate the CO_2 response runs between REM and NREM sleep from one sleep cycle to the next. Arousal was not defined per se, except as changes in EEG, and arousal seemed to be used synonymously with waking.

The ventilatory response to CO_2 during NREM sleep was orderly and predictable, with progressive increases in tidal volume and respiratory frequency as alveolar (end tidal) CO_2 concentration increased. In contrast, the pattern of breathing during REM sleep was very irregular and remained so during CO_2 rebreathing. The duration of rebreathing before arousal was longer and more variable in REM sleep than in NREM (1.71 vs. .99 minutes, respectively, $p<.05$), despite initially comparable levels of mixed venous carbon dioxide pressures and comparable rates of increase in $PACO_2$ concentration. The $PACO_2$ at the point of arousal was considerably higher in REM than in NREM sleep (60.3 vs. 54.2 torr, respectively, $p<.05$). Breath-by-breath analysis of ventilation during CO_2 rebreathing by least squares regression revealed regression coefficients (slopes) of minute ventilation, tidal volume and respiratory frequency against $PACO_2$ were significantly reduced in REM sleep. In many instances, the regression coefficients were not different from zero. During REM sleep the correlation coefficients between these same variables ranged from .26 to .46, compared to .71 to .91 during NREM sleep.

The specific $PACO_2$ at the point of arousal during NREM sleep was only slightly above the normocapnic venous carbon dioxide with a mean difference of 7.6 torr. In the rebreathing technique there is a significant CO_2 difference between arterial blood, cerebrospinal fluid or brain tissue, with the magnitude varying with the rate of CO_2 increase (Read & Leigh, 1967). With a rapid increase in alveolar CO_2 pressure during rebreathing, the CO_2 pressure of the cerebral structures involved in the arousal reaction was likely to be less than the $PACO_2$ and may, in fact, have been only minimally above the normal venous CO2 pressure. As long as arterial CO_2 remains less than normal venous CO_2 during rebreathing, increases in cerebral blood flow theoretically will compensate for arterial hypercapnia and allow maintenance of normal brain CO_2 concentration (Read & Leigh, 1967). However, once the arterial CO_2 is equal to normocapnic venous CO_2, the CO_2 concentration of the brain must increase. It appears that as soon as this condition prevails in NREM sleep, arousal occurs. This would account for the consistent observation that the arterial CO_2 pressure was only slightly greater than the normocapnic venous CO_2 pressure. This correlates with observations in humans that slowly developing hypercapnia (3-4 torr per minute) invariably leads to arousal from NREM sleep at an alveolar CO_2 of 50 torr. (Bulow, 1963).

In contrast, CO_2 rebreathing continued for a significantly longer time during REM sleep and reached significantly higher CO_2 concentrations before the animal awakened. These findings suggest that the cerebral areas involved with arousal were either unaware of the stimulus or were unable to respond to it. Arousal thresholds for acoustical stimuli are known to be increased during REM sleep (Jouvet,

1965). Thus, impaired arousal due to hypercapnia appears to be a manifestation of a more generalized phenomenon that characterizes REM sleep, and one that could have important clinical implications.

Ventilatory and Waking Responses to Hypoxia

The waking and ventilatory response to hypoxia has been the focus of several studies in animals during the past decade. The waking and ventilatory responses to acute hypoxia during REM and NREM sleep was investigated in four dogs (Phillipson, Sullivan, Read, Murphy & Kozar 1978). The dogs were prepared as in the study by Phillipson, Kozar, Rebuck, et al. (1977) described earlier, and the studies were performed during a regular afternoon nap. Sleep stages were determined by ECG and behavioral criteria. Measurements of waking and ventilatory responses to hypoxia during NREM were confined to periods of high voltage ECG waves of 2-4 hz. Measurements during REM were confined to periods characterized by ECG patterns of REM, visible REM, and twitching ears, nose, lips, and limbs. Arousal during progressive hypoxia was indicated by ECG and behavioral change during NREM sleep; and primarily, by behavioral changes during REM sleep. Progressive hypoxia was induced by having the dogs rebreathe from a Wedge spirometer (Med Science) that initially contained 3-5 liters of a gas mixture of 8%-10% O2 in balance nitrogen. Preliminary work with each dog determined the precise concentration of O_2 and volume of gas mixture in the spirometer that would result in a progressive drop of oxygen saturation to 75% in about 1 minute of rebreathing. That same concentration and volume was then used throughout the study. Alveolar CO2 concentrations were kept

constant at the eucapnic level (± 1 torr) during hypoxia. Each rebreathing experiment was continued until the animal awoke, which invariably occurred within 3 minutes. Sleep usually resumed shortly after resuming breathing room air, allowing for serveral rebreathing cycles to be obtained on the same day. Oxygen saturation was measured by an ear oximeter (Hewlett Packard 47201A).

During progressive hypoxia in NREM sleep with a normal $PACO_2$ for that sleep state, arousal occurred at 0.53 minutes of rebreathing at an average oxygen saturation of 87.5%. In contrast, during REM sleep, with a normal $PACO_2$, arousal did not occur until 1.15 minutes, when oxygen saturation had decreased to an average of 70.5%. To examine the interaction of CO_2 and hypoxia on ventilatory and waking responses, the rate of flow through the CO_2 absorber was altered to provide CO_2 values above and below the eucapnic levels. During NREM sleep there was a clear interaction between $PACO_2$ during hypoxia and waking oxygen saturation, so that the higher the $PACO_2$, the higher the oxygen saturation at the time of arousal. During REM sleep, the $PACO_2$ during rebreathing had little influence on oxygen saturation at awakening.

The instantaneous minute volume of ventilation in response to eucapnic hypoxia was similar during waking, NREM and REM sleep. The level of $PACO_2$ during hypoxia had little effect on the response of minute ventilation to hypoxia during REM sleep; but, during NREM, there was a marked ventilatory interaction between CO_2 and hypoxia. Thus, there appears to be a fundamental difference in the ventilatory responses to chemostimulation during REM sleep, with the response to CO_2 being diminished and the response to hypoxia remaining intact. In this study, the arousal threshold in response to hypoxia was increased during

REM sleep. Increased arousal thresholds during REM sleep have also been shown in response to acoustic stimuli (Jouvet, 1965) and to hypercapnia (Phillipson, Kozar, Rebuck, et al. (1977). The specific mechanisms underlying these changes is not clear; however, arousal due to hypoxia, presumably, relates to cortical stimulation secondary to reticular formation excitation by afferent impulses from the peripheral chemoreceptors. Since the ventilatory response to hypoxia during REM sleep remained intact, the sensitivities of the chemoreceptors and medullary respiratory neurons likely were unchanged. These authors concluded that the increased arousal threshold to hypoxia was likely due to influences acting at higher cerebral or cortical levels.

The studies discussed above were undertaken on tracheotomized adult dogs. The influence of the upper airway reflexes in contributing to the arousal response were not addressed. Nasopharyngeal sensors may play a role in mediating arousal responses (Bowes, 1984).

Arousal Response to Upper Airway Obstruction

Repeated obstruction of the upper airway during sleep may adversly affect the arousal response. This is important in patients with obstructive sleep apnea because these obstructive events are terminated by behavioral and EEG evidence of arousal followed by restoration of upper airway patency and resumption of tidal ventilation. Repeated obstructions of the upper airway were carried out in 5 chronically instrumented and tracheotomized lambs between and 8 and 14 days of age (Fewell, Williams, Szabo, & Taylor, 1988). The following variables were monitored: oxygen saturation, arterial blood pressure, ECG, nuchal and

diaphragmatic EMG and EOG. All data were recorded on a Grass Model 7 polygraph (Grass Medical Instruments). The upper airway was obstructed each time the lamb went to sleep for approximately 100 sleep epochs. Control measurements were made prior to each experimental upper airway obstruction. Airway obstruction was terminated during the experimental period when the animal aroused from sleep. For statistical analysis, data from the first five upper airway obstructions in each sleep state were compared to the data from the last five upper airway obstructions in each sleep state to determine the effect of repeated upper airway obstruction.

Arousal occurred from both sleep states during upper airway obstruction, but was significantly ($p < 0.05$) delayed during active sleep compared to quiet sleep. The time to arousal was increased ($p<0.05$) and the oxygen saturation was decreased by repeated upper airway obstruction in active sleep. Heart rate decreased and respiratory rate tended to decrease during upper airway obstruction before arousal in both sleep states. There were no significant changes in blood pressure.

These results provide evidence that the arousal response to a respiratory stimulus during sleep, changes after repeated exposure to the stimulus. It is thought that the arousal response from active sleep is primarily mediated by the peripheral chemoreceptors in response to hypoxemia, and this mechanisms appears to change after repeated stimulation. The arousal response from quiet sleep during upper airway obstruction may be mediated by lung or chest wall mechanoreceptors and does not appear to change after repeated stimulation. These findings support the hypothesis that if patients are repeatedly exposed to hypoxemia, either from multiple apneic episodes or during sleep from

gas-exchange abnormalities, the arousal response to apnea might be impaired. A delayed arousal from active sleep, as found in this study, might have more profound consequences for newborns, and especially prematures, since prematures spend approximately 65-80% of total sleep time in REM sleep (Parmelee, Wenner, Akiyama, et al., 1967). Although there were no significant changes in blood pressure found in this study, acute increases in blood pressure alone have been shown to produce arousal from both sleep states in lambs (Fewell & Johnson, 1984).

Arousal Response to Acute Hypoxemia

More recently the arousal response to rapidly developing hypoxemia in newborn lambs (as opposed to adult animals) during quiet and active sleep was investigated (Fewell & Baker, 1987). The chronically instrumented lambs were initially given 21% O_2 to breathe via a tracheostomy tube; inspired oxygen concentration was then alternatively decreased to 10%, 5%, or 0%. The sequence of gases was alternated on an hourly basis to avoid any sequence effects and the sequence was changed between animals. Electrophysical criteria were used to define arousal from sleep; for quiet sleep the point of arousal was determined by a change in the ECG from a high voltage slow wave pattern to a low voltage-fast wave pattern; for active sleep the point of arousal was determined by a return of tonic activity on the nuchal EMG. All data were recorded on a Grass Model 7 polygraph (Grass Medical Instruments) and the lambs were monitored on a closed circuit video system. Control measurements were made while the lambs were breathing 21% O2 and experimental measures were made during breathing of 10%, 5% or 0% O2.

At least 2 epochs of quiet sleep and active sleep were collected at each different hypoxic challange in each animal. The inspired oxygen concentration was returned to 21% if (1) the animal did not arouse within 2 minutes after being subjected to the lowered oxygen concentration; or (2) if electrocortical signs of cerebral hypoxia occurred; or (3) if the animal aroused from sleep.

When breathing 10%, 5%, or 0% O2 the rate of decrease in oxygen saturation was not affected by sleep state. However, the arousal response to rapidly developing hypoxemia was affected by sleep state. During quiet sleep, arousal occurred at similiar oxygen saturations; that is at 10% 5% and 0% inspired O2 concentration, the oxygen saturation values were 81%, 80% and 83% respectively, despite the different rates of decreases in oxygen saturation that occurred with breathing different oxygen mixtures. This suggests that arousal occurred once an arousal threshold had been reached. During active sleep, however, arousal occurred at different oxygen saturations; that is at 10%, 5% and 0% inspired oxygen the oxygen saturation values were 76%, 55% and 44% respectively. This suggests that arousal occurred following an arousal latency, once an arousal threshold had been reached. During some epochs of active sleep (13% in 2 lambs on 5% oxygen and 48% in 6 lambs on 0% oxygen) the ECG changed from a fast wave-low voltage pattern to a slow wave-high voltage pattern before the animal aroused. These slow wave patterns are thought to be secondary to cerebral hypoxia. Thus, if the rate of change of oxygenation is great enough during an apneic episode during active sleep, then arousal may fail to occur before electrocortical signs of cerebral hypoxia and primary apnea occur. If, in addition, the gasping reflex, which follow

primary apnea, were impaired, or circulation failed, death could quickly ensue.

Arousal Response Following Repeated Episodes of Acute Hypoxemia

Does repeated exposure to rapidly developing hypoxemia influence the interaction between oxygen and carbon dioxide in causing arousal from sleep? In a series of experiments Fewell and Konduri (1988) exposed one group (n = 5) of chronically instrumented lambs to 5% O2 during approximately 100 epochs of sleep over a period of approximately 24-48 hours, until they aroused. These lambs were subsequently given gas mixtures of 5% O_2 plus, either 0%, 5% or 10% CO_2 to breathe. The gas mixtures were alternated on an hourly basis to avoid any sequence effects and the sequence was changed between animals. Lambs without prior exposure to the multiple episodes of rapidly developing hypoxemia, (n = 7) but who were exposed to the gas mixtures of 5% O_2 and the three varying concentrations of CO_2 during the experimental period served as a comparison group.

In lambs not previously exposed to rapidly developing hypoxemia, there was a slight interaction between oxygen and carbon dioxide in initiating arousal in quiet sleep only. Repeated exposure to rapidly developing hypoxemia did influence the arousal response in both quiet and active sleep; there was increased time to arousal and decreased oxygen saturation at arousal. In those previously exposed to rapidly developing hypoxemia, the time to arousal decreased and the oxygen saturation at arousal increased as increasing amounts of CO_2 were added to the hypoxic gas mixture. This suggests that a greater interaction

exists between O_2 and CO_2 in initiating arousal, especially in active sleep, once an arousal response decrement has developed to hypoxemia alone. Thus, once the arousal response adapts to one stimulus, such as oxygen, another stimulus, such as carbon dioxide may take the dominant role in initiating arousal. These results may have implications for all patients who experience episodes of hypoxemia during sleep. However, it is important to keep in mind that extrapolation of data obtained from young mammals to human newborns may not be appropriate since sleep state maturation may be species related (Woods, Egbert, & Geis, ****).

Arousal Studies in Adults

Arousal and Ventilatory Responses to Hypoxia in Healthy Adults

The arousal and ventilatory responses to hypoxia in normal, sleeping adults were investigated by Berthon-Jones and Sullivan (1982). Responses of nine healthy volunteer subjects were measured in a sleep laboratory while awake, and during REM and NREM sleep. Sleep stages were monitored by ECG, EOG and submental EMG. Wakefulness was defined by behavioral criteria, the presence of low voltage mixed frequency ECG, tonic EMG, and rapid eye movements. NREM sleep was defined by low EMG tone, slow or absent eye movements, and presence of high voltage slow waves. REM sleep was defined by awake type EEG, atonic EMG with phasic bursts, and rapid eye movements, both visually and on EOG. Arousal from NREM sleep was identified by desynchronization of the EEG recordings and return of tonic EMG activity. Arousal from REM sleep was identified by return of sustained tonic EMG. Oxygen saturation was measured by an ear

oximeter (Hewlett Packard Model 47201A). End tidal carbon dioxide tension was measured with a rapid infrared analyzer (Godard capnography). Tidal volume was calculated by electronic integration of the pressure across a pneumotachygraph (Statham PM 15 ETC transducer) attached to a hermetically sealed face mask. Progressive hypoxia was induced while end tidal carbon dioxide concentration was kept constant by using a modification of a rebreathing technique.

A total of 77 tests of responses to hypoxia were performed on the nine subjects; 36 during wakefulness, 6 in Stage II NREM, 20 in Stages III and IV NREM, and 15 in REM sleep. The degree of oxygen saturation at the moment of arousal from sleep varied with each subject. The most striking observation was that, regardless of sleep state, in approximately one half of the tests, the subject failed to awaken before the test was terminated at the agreed-upon cutoff point of 70% oxygen saturation (PaO_2 = 37 torr). Arousal failed to occur before 70% oxygen saturation in 46% (12/26) hypoxic tests in NREM sleep and in 47% (7/15) of hypoxic tests in REM sleep. Consistency in responses to the hypoxic challenge was demonstrated by only three subjects; two who consistently failed to arouse by 70% oxygen saturation and one who consistently aroused before 70% oxygen saturation. Otherwise, the subjects showed a wide intraindividual range in arousal threshold, regardless of their sleep state.

There was no evidence of a progressive change in sleep stage during the hypoxic tests. When arousal occurred, it did so as a sudden transition from a previously consistent sleep stage. Since arousal frequently did not occur in either REM or NREM, it was not possible to identify a difference in arousal threshold in these two states. It is

possible that such a difference would emerge, if the progressive hypoxia were continued below 70% saturation. That arousal from either REM or NREM sleep failed to occur in nearly one half the tests performed before 70% oxygen saturation is in contrast to findings in adult dogs that oxygen saturation of 80-90% consistently produced arousal from NREM sleep, but levels of 70% oxygen saturation were consistently reached prior to arousal from REM sleep (Phillipson, Sullivan, Read, et al., 1978).

In Berthon-Jones and Sullivan's (1982) subjects the ventilatory responses to progressive hypoxia, with carbon dioxide held constant, averaged 0.68 L/min/% decrease in oxygen saturation during the awake state. This was reduced during NREM sleep (mean, 0.42L/min/% saturation) and further reduced during REM sleep (mean, 0.33L/min/% saturation). The ventilatory response slopes were significantly different between awake and REM and NREM sleep; however, there was no significant differences between REM and NREM sleep. For all states, the ventilatory response to progressive hypoxia was achieved by a progressive increase in tidal volume.

The degree of partial pressure of arterial oxygenation known to cause central nervous system malfunction depends on a number of factors, including brain blood flow, glucose concentration and carbon dioxide tension. At an oxygen saturation of 70% there usually is ECG evidence of central nervous system dysfunction; whereas, various tests of cognitive function show impairment at levels well above 70% oxygen saturation (Gibson, Pulsinelli, Blass, & Duffy, 1981; Rebuck, Davis, Longmire, Upton, & Powles, 1976). A possible explanation for the decreased hypoxic arousal response seen in some normal human subjects

might be that the arousal-promoting elements of the reticular activating system are particularly prone to depression by hypoxia. Severe hypoxia causes sudden unconsciousness with little warning in the awake state (Gibson, Pulsinelli, Blass, et al. 1981). Rapid onset of de-saturation might preclude arousal since there appears to be very little safety margin in the balance between hypoxic-induced arousal and brain depression.

Effect of Sleep State on Ventilatory and Arousal Responses to Hypercapnia in Healthy Adults

In patients with obstructive sleep apnea syndrome, asphyxia from total airway occlusion produces arousal in REM much later than in NREM sleep (Sullivan & Issa, 1980). Berthon-Jones and Sullivan (1984) investigated the effect of sleep state on ventilatory and arousal responses to induced hypercapnia in 13 healthy adults. Sleep state was monitored as described above (Berthon-Jones & Sullivan, 1982). The subjects rebreathed from a bag initially containing 7% CO_2 and 40% O_2 via a hermetically fitted nose mask. When the subject had been in the desired sleep state for at least 2 minutes, a CO_2 rebreathing test was performed, and the end tidal CO_2 pressure was allowed to rise until obvious behavioral arousal occurred. After several tests during sleep, control tests were performed after the test-induced arousal during wakefulness.

A total of 169 nighttime trials were conducted. The arousal response during NREM always was abrupt and clear-cut, with essentially simultaneous behavioral, EMG and EEG changes. During tests conducted in

NREM sleep, there was no change in sleep state until arousal occurred. During REM the process was less predictable, with the subjects showing a transient arousal with the onset of rebreathing but continuing in REM sleep until final arousal (21 cases), changing to NREM sleep (2 cases), or awaking abruptly with the onset of rebreathing (11 cases). Transient arousals were not present in NREM sleep and the interval between transient, and final arousal varied greatly but was less than 30 seconds in 11 cases. The arousal threshold, as indicated by $PACO_2$ at arousal, time to arousal, and minute ventilation at arousal, all increased with deepening NREM sleep and was decreased during REM sleep in the male subjects. The mean $PACO_2$ at arousal in NREM sleep in males was 58 torr in Stage II, 63 torr in Stage IV, and was 57 torr in REM sleep. Females showed no significant change in arousal alveolar PCO_2 during different sleep stages. In this study, arousal occurred after an increase in $PACO_2$ of about 6 torr. Animal studies have also documented a higher PACO2 at the point of arousal during REM compared to NREM sleep (Phillipson, Kozar, & Rebuck, et al 1977). This study supports the findings of others (e.g., Bulow, 1963; Douglas, White, Weil, Pickett, & Zwillich, 1982) that hypercapnia is a potent arousal stimulus in all sleep states. Ventilatory responses in males decreased by 49% from baseline in NREM sleep and by 69% in REM sleep, whereas ventilatory responses in females were not significantly affected by sleep state.

Arousal Response to Occlusion of the Upper Airway during Sleep

Occlusion of the upper airway during sleep is defined as obstructive sleep apnea. The airway occlusion is the result of suction

collapse of the oropharyngeal airway during inspiration (Remmers, de Groot, Sauerland, & Anch, 1978) and once occluded, it remains so until arousal from sleep, despite increasing respiratory effort. The increase in airway muscle tone brought about by arousal is probably the dominant mechanism terminating obstructive sleep apnea (Remmers, de Groot, Sauerland, et al., 1978; Sullivan & Issa, 1980). The difference in apnea durations in NREM and REM sleep in adults has been attributed to a difference in arousal thresholds (Issa & Sullivan, 1982; Phillipson, Murphy, & Kozar, 1976).

The arousal response to total airway occlusion in 13 normal adults was investigated during an overnight sleep study by Issa and Sullivan (1983). Sleep state was determined by EEG, chin EMG, and EOGs. Oxygen saturation was measured by an ear oximeter (Hewlett-Packard 47201A). Electrocardiogram and heart rate were monitored continuously. Rib cage and abdominal wall motion were recorded using a respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring, Inc.) Diaphragm EMG were recorded by a pair of silver-silver chloride electrodes. Total airway occlusion during sleep was induced by inflating a small pair of soft rubber balloons, positioned on each side of two rigid tubes, which were connected proximally to Teflon tubes fitted in each nostril and distally to a valveless breathing circuit. A minimum of 5 minutes of consistent sleep was allowed before the occlusion test was performed.

Arousal from NREM sleep was determined by the sudden desynchronization of the ECG and the return of chin muscle EMG activity. Arousal from REM sleep was determined by the sustained return of EMG activity. In addition, each subject was instructed at each arousal, to give a hand

signal to indicated full alertness. After each occlusion-arousal trial, the subject was allowed to return to sleep, thus providing several trials for each subject in one night. The responses to total airway occlusion during sleep were analyzed from 39 tests performed during stage III/IV NREM sleep in 11 subjects and from 10 tests during REM sleep in 5 subjects.

The duration of total airway occlusion tolerated in NREM sleep before arousal was induced (as measured from the onset of the first occluded inspiration to the point of ECG arousal) was variable within and between subjects, with a range of 0.9-67 seconds. During 9 tests, subjects awoke during or immediately after the first occluded breath (range 0.9-5 seconds); however, all subjects had occlusion tests during which arousal occurred only after a prolonged period (range 11-67 seconds) and in which there were multiple breathing attempts with a fall in the oxygen saturation (range 2-18%). Arousal did not occur at any specific time of the respiratory cycle; with 23 tests, arousal coincided with the inspiratory effort; whereas, in 16 cases, arousal occurred during the expiratory phase.

During all the tests, the high voltage ECG pattern did not change until the point of arousal. The peak suction pressure of the first occluded breath varied within and between subjects. When arousal did not occur immediately, the peak pressure increased progressively with each successive inspiratory effort. The mean fall in oxygen saturation during occlusion in NREM sleep was 4.2% (range 0-18%). During REM sleep arousal occurred within 6.2 seconds (range 0.9-11.8 seconds) after the onset of the first occluded breath. These short-latency arousal responses were significantly different from the group mean in NREM sleep

of 20.4 seconds ($p<.001$). During REM sleep, arousal occurred after 10 seconds in 10% of trials whereas during NREM sleep arousals occurred after 10 seconds in 76% of trials. In all of the trials, there was an abrupt change to wakefulness, with no ECG evidence of alteration to another sleep state within the test. The mean fall in oxygen saturation during airway occlusion in REM sleep was 1.2%. In all 10 tests, during REM sleep total airway occlusion induced a rapid, shallow breathing response, which ceased as soon as arousal occurred, even though nasal occlusion was sustained. This pattern was absent during REM sleep without occlusion. In contrast to the pattern of progressive airway pressure increases in response to airway occlusion during NREM sleep, during REM sleep the response was erratic and irregular. The airway pressure prior to arousal during REM sleep did not represent the maximum pressure reached during the course of the occlusion.

To determine the number of arousals that might have occurred without the nasal occlusion tests, another sleep study was performed on 3 subjects arbitrarily selected from the group. Sham tests of rapid deflation-inflation were performed repeatedly throughout the night. Arousals occurring within 67 seconds during NREM sleep and within 11 seconds of REM sleep in response to the sham test were examined. These times were chosen because they represented the longest duration of nasal occlusion tolerated before arousal during NREM and REM sleep trials, respectively. Of the 159 sham tests performed during NREM sleep, 9 arousals occurred during this period, compared with 39 arousals during 39 trials. The probability that spontaneous arousals accounted for the pattern of response in NREM sleep was $p<.001$ (binominal distribution test). During REM sleep, only 4 arousals occurred within 11 seconds

during 84 sham tests, compared to 10 arousals in response to 10 occlusion tests ($p<.001$, binominal distribution test). The longest duration at which arousal occurred following a sham test was found to be 5.2 seconds in NREM sleep and 3.5 seconds in REM sleep. If these arousals were caused by the procedure itself, then the ratios of 9:159 in NREM and 4:84 in REM sleep, estimate the proportion of spurious arousals in the nasal occlusion tests. During the total occlusion tests in NREM, there were 9 arousal responses within 5.2 seconds in 39 tests. These were not accounted for by the expected number of spurious arousals ($p<.001$, binominal distribution test). Similarly, the REM data of 4 arousals within 3.5 seconds were not accounted for by the expected number of spurious arousals (4 out of 84 tests, $p<.05$, binominal distribution). The purpose of the Issa and Sullivan study was not to identify the mechanisms causing arousal. The responses during NREM sleep were usually an ordered and progressive breath-by-breath response to asphyxia, followed by an abrupt transition to wakefulness at some threshold level of asphyxia. However, there also were responses in which arousal occurred during or soon after the first occluded breath, at a time when asphyxic stimuli would be minimal. The arousal responses in NREM were very variable in relation to the duration of the occlusion test. This wide scattering of the data suggests the presence of two major afferent systems producing arousal from NREM sleep in response to airway occlusion, with the short latency responses being fast mechanoreceptor input from the upper airway and the slower responses being from the chemoreceptors. The results during REM sleep were unexpected and contrary to the findings in patients with obstructive

sleep apnea and to findings in dogs with tracheal occlusion, in which the REM-apneic durations were prolonged compared to NREM sleep. Both tracheotomized dogs and adults with obstructive sleep apnea produced large changes in airway pressure which are not transmitted to the nasal airway. Pressure sensitive receptors in the upper airway play a critical role in maintaining oropharyngeal muscle tone in rabbits (Wilson, et al. 1980). In Issa and Sullivan's study (1983), the suction pressures were transmitted to the nasal airway, where mucosal mechanoreceptors may be involved. The authors do not address the issue of whether the length of time before arousal was related to the multiple trials each subject experienced.

Arousal Mechanisms in Obstructive Sleep Apnea

In adults with obstructive sleep apnea (OSA) syndromes the airway walls and tongue are thought to become atonic during all sleep or REM sleep with the airways becoming closed by negative intra-airway pressure during inspiration. The role of arousal mechanisms in five patients with obstructive sleep apnea was investigated (Sullivan & Issa, 1980). No patients had major lung disease, but all presented with excessive daytime sleepiness, noisy snoring, and body weight between 120% and 150% of ideal weight. Three had no definable upper airway pathology by direct examination or radiographic study; one had gross enlargement of the tonsils, and one had acromegaly. All night sleep studies were done with continuous recording of heart rate, ECG, EMG (submental and nuchal), and rapid eye movements. Respiratory variables recorded included oxygen saturation (Hewlett-Packard, 47201A), abdominal and

chest wall movements by impedance pneumography and an uncalibrated index of oropharyngeal airflow (thermistor or pressure transducer inserted into a face mask). Signals were recorded on an eight-channel pen recorder (Hewlett-Packard 7758A or Grass 7D polygraph) or a multichannel storage oscilloscope (Tektronix 5113N). All subjects demonstrated the typical repetitive pattern of obstruction, progressive asphyxia, followed by relief from obstruction. All had longer periods of apnea in unequivocal REM sleep compared to NREM sleep. The duration of apnea was longer and the minimum level of saturation was consistently lower in REM sleep. Direct evidence that arousal from sleep is the key factor in terminating upper airway occlusion was: 1) the invariable occurrence of increased EMG activity in non-respiratory postural muscles (e.g., submental and nuchal muscles) just prior to the relief of occlusion and 2) the frequent occurrence of gross body movements. There was an onset of slow waves in the ECG just prior to the end of the apnea which may indicate a progression into NREM sleep in the limited amount of time available to the patient between repetitive arousals; or, alternatively, such slow waves could be the result of brain hypoxia. During REM sleep oxygen saturation at the time of arousal ranged from approximately 40% to 75%, compared to NREM sleep during which the oxygen saturation ranged from approximately 60% to 85%. The fact that oxygen supplementation lengthens obstructive sleep apnea suggests that hypoxia is the stimulus causing arousal (Motta & Guilleminault, 1978). If an arousal response is the crucial factor terminating an obstructive apneic event, it presumably does so by causing a return of postural muscle activity in the tongue and pharyngeal muscles or by providing an additional drive to the muscles of inspiration. The findings of Sullivan and Issa (1980)

are supported by a study of patients with acquired micrognathia, a condition which is frequently associated with obstructive apneas during sleep. The oxygen saturation near the point of arousal was consistently lower during REM than during NREM sleep (mean 77% vs. 86%, respectively) (Coccagna , di Donato, Verrucchi, Cirignotta, Mantovani & Lugaresi, 1976).

Arousal Time in Response to Airflow Obstruction

Some patients with chronic severe bronchial asthma have nocturnal bronchospasm and do not awaken until severe bronchoconstriction has occurred which may lead to cardio-respiratory arrest. The time to arousal, following airway occlusion at end expiration during sleep, was examined in two adolescent males with bronchial asthma who were clinically stable at the time of the study (Hudgel, Kellum, Martin & Johnson, 1982). Three healthy males served as a comparison group. One asthamatic subject had a significantly prolonged time to arousal (20 seconds) during stage 3-4 NREM sleep compared to stage 2 NREM and to REM sleep. The other asthamatic subject had a significantly prolonged time to arousal (26 seconds) in REM compared to NREM sleep. The healthy subjects had arousals times of less than 10 seconds in both sleep state. Thus, a decreased arousal response may play a role in fatal nocturnal asthma.

Arousal Studies in Infants

Arousal and Ventilatory Response to Hypoxic and Hypercarbic Challenges

Arousal and ventilatory responses to hypoxia and to hypercarbia are used by researchers and by clinicians as a way to detect possible functional abnormalities of cardiorespiratory control during sleep in infants. The overall purpose of these studies is to try to develop more specific and sensitive predictors of subsequent significant apneas and of SIDS.

The hypercarbic and hypoxic arousal response was assessed in infants who had experienced an apparent life threatening event (ALTE) and in a group of normal infants (McCulloch, Brovillette, Guzzette, & Hunt, 1982). Infants having an episode of ALTE which can not be explained on the basis of any underlying condition are diagnosed as having apnea of infancy; overall approximately 7% of SIDS victims are thought to come from this group of infants (Hoffman, Damus, Krongrad, & Hillman, 1986). An ALTE was defined in the McCulloch, Brovillette, Guzzett, et al. study as an episode of sleep-related cyanosis or marked pallor associated with limpness, and/or an observed interval of apnea which required vigorous stimulation or mouth-to-mouth resuscitation. Each subject underwent a hypercarbic and a hypoxic challenge; the order of which was randomly determined. The mean age of the subjects at the time of the study was 7.3 weeks (normals) and 9.3 weeks (ALTE).

Testing occurred during natural, post-prandial sleep. Baseline recordings were made for at least 3 minutes during NREM sleep, as evidenced by a regular nasal airflow pattern, chest and abdominal

excursions in-phase, and absence of spontaneous body or eye movements. A recovery period of at least 10 minutes was provided between the two challenges. Hypoxic arousal was assessed via successive increments of 15% O_2 added to the inspired air mixture. Total flow into the oxygen-hood was kept constant. At each new fraction of inspired oxygen (FIO_2) monitoring was continued for 1 minute after a stable transcutaneous oxygen value (± 1 torr) had been reached. If arousal did not occur prior to reaching an FIO_2 of 0.15, the subject was maintained at this FIO_2 for a maximum of 20 minutes. Assuming a normal alveolar-arterial PO_2 difference, the minimum PaO_2 reached should not have been less than 45 to 50 torr, which would correspond to an oxygen saturation in the 80% range. Hypoxic arousal was considered to be absent if arousal had not occurred after 20 minutes. If arousal did occur, the inspired oxygen concentration was abruptly increased until the infant resumed sleeping and a repeat arousal challenge was attempted. The inspired oxygen concentration increased one step higher than that which produced arousal. Whenever more than one measure of hypoxic arousal was obtained, the mean was used for statistical analysis.

Hypercarbic arousal response was assessed by a progressive step-wise increment in the fraction of inspired carbon dioxide ($FICO_2$). After baseline recordings, 0.12 $FICO_2$ was added to the inspired air mixture and connected to an oxygenhood until $PACO_2$ reached 40 torr. After a 3-minute interval at this level, increasing amounts of 0.12 FICO2 were added to achieve successive 5 torr increments in $PACO_2$.

Alveolar carbon dioxide was measured by a nasal cannula attached to a carbon dioxide analyzer (Cavitron). Hypercarbic breathing was continued for 3 minutes at each new level of $PACO_2$ (5 torr increments)

until arousal occurred or until a maximum $PACO_2$ of 65 torr was reached. Total inspired flow was kept constant. The criteria for arousal were eye opening and crying. These were not subtle changes, but were always obvious abrupt changes in state. When arousal occurred, $FICO_2$ was abruptly lowered until the subject resumed sleeping. The $PACO_2$ level was maintained one step less than that which produced arousal, and a repeat hypercarbic arousal response was attempted. Whenever more than one measure of arousal threshold was obtained, the mean was used for statistical analysis. In the McCulloch and colleagues study, hypoxic arousal was assessed in all ALTE subjects and in 20 out of 22 of normal subjects. In two of the normal subjects, hypercarbic arousal challenges had been performed first, and sleep could not be reestablished for hypoxic arousal challenges. During the hypoxic challenge, the maximum transcutaneous oxygen decrease from baseline was not significantly different between the two groups (29 torr, ALTE vs. 22.8 torr, normals). Despite this lower minimum transcutaneous oxygen level induced in ALTE subjects hypoxic arousal could be achieved in only 1 out of 11 subjects, compared to 14 out of 20 of the normal subjects ($p<.01$). In the one ALTE subject who did arouse to hypoxia, the hypercarbic arousal threshold was 61 torr, which was higher than in any normal subject. An assessment of hypercarbic arousal was obtained in all 11 ALTE subjects and in 19 out of 22 of the normal subjects. For three of the normal subjects sleep could not be reestablished for hypercarbic testing following hypoxic arousal testing. All 19 normal subjects and 10 out of 11 of those with ALTE aroused from sleep in response to the hypercarbic stimulus. The mean $PACO_2$ level at which arousal occurred was 48.8 torr in normal subjects compared to 54.9 torr in the ALTE subjects ($p<.05$).

In the one ALTE subject in whom hypercarbic arousal was absent, a $PACO_2$ of 58 torr was achieved.

The two groups did not differ significantly in mean age at the time of the study, in baseline respiratory rate, $PACO_2$, or transcutaneous oxygen values. The mean rate of increase in $PACO_2$ during hypercarbic challenges and the mean rate of decrease in transcutaneous oxygen values during hypoxic challenges were not significantly different in the two groups. Neither the magnitude of the increase in transcutaneous oxygen values which occurred in response to hypercarbic hyperventilation (25 torr in normals vs. 31 torr in ALTE) nor the decrease in $PACO_2$ which occurred in response to hypoxic hyperventilation (1.2 torr normals vs. 0.6 torr ALTE) were significantly different.

Hyperventilatory responses to hypercarbia and to hypoxia occurred in all subjects and was related to progressive increase in $FICO_2$ and FIO_2, respectively, and was not temporally related to the arousal response. Irregular, non-phasic breathing patterns did occur in both groups, but were brief and were not present at the time of arousal. This breathing pattern also was not present in any subject at the time that hypoxia arousal responsiveness was concluded to be absent. During the hypoxic challenge, the two groups did not differ in respiratory rate, in episodes of periodic breathing per 100 minutes, or in frequency of apneic pauses equal to or greater than 3 seconds (expressd as a percent of total sleep duration, A3/D%). This arousal response study was not designed to detect prolonged sleep apneas, and none were observed during these daytime sleep assessments. Infants who have had an ALTE have been observed to have a greater number and duration of apneic episodes than normal infants when assessed during nocturnal sleep (Guilleminault, Tilkian & Dement, 1976; Guilleminault, et al. 1981).

The minimum transcutaneous oxygen value reached in the McCulloch and co-workers' study was generally greater than 40 torr, corresponding to an oxygen saturation of approximately 75%; and most infants were at this minimum transcutaneous level for 4 to 6 minutes prior to arousal. The baseline data were collected while the subjects were in NREM sleep; however, the sleep state was not further assessed during the study and no observations were made in relation to arousal and sleep state. Arousal responsiveness has been noted to be diminished in REM sleep compared to NREM sleep in animals (Henderson-Smart & Read, 1979b; Jeffrey & Read, 1980; Phillipson, Kozar, Rebuck, & Murphy, 1977; Phillipson, Sullivan, Read, et al., 1978).

The hypercapnic and hypoxic arousal response in normal subjects and subjects with ALTE was also investigated by van der Hal, Sargent, Platzker, and Keens (1982). For this study an ALTE was defined as the occurrence of limpness, cyanosis, and apnea requiring vigorous stimulation or resuscitation for which no treatable etiology could be found. The ALTE group (n = 15) had their initial episode at 2.7 months (mean age) and were studied at 4.1 months (mean age) while still having recurrent apneas. The control group of normal subjects (n = 6) were 10.9 months (mean age) at the time of the study. For hypoxic arousal, the pressure of inspired oxygen was rapidly decreased during quiet sleep to 74 ± 1 torr unless arousal occurred. The criteria for arousal were restlessness, agitation, and eye opening. All normal subjects aroused to hypoxia (PIO_2 76 ± 1 torr) while only 9 out of 15 subjects with ALTE aroused to hypoxia (PIO_2 74 ± 1 torr). In response to hypoxia, the normal subjects had more hyperpnea than the ALTE subjects (change in $PACO_2$ 5.5 torr vs. 3.8 torr, respectively, $p<.025$).

During hypercarbic challenges, the pressure of inspired carbon dioxide was rapidly increased during quiet sleep to 60 torr, unless arousal occurred. All normal and ALTE subjects aroused in response to the hypercarbic challenge; however, the $PICO_2$ was greater at arousal in ALTE subjects compared to normal subjects (44 vs. 38 torr, respectively, $p<.025$). These findings suggest that ALTE infants have decreased responses to hypoxia and hypercapnia. These authors suggested that infants with an abnormal hypoxic arousal response have more frequent and severe subsequent apneic episodes. Therefore, an abnormal hypoxic arousal response might identify infants at highest risk for subsequent apnea.

In contrast to the above findings, Ariagno, Nagel and Guilleminault (1980) have found no difference in arousal response between normal infants and those with previous episodes of ALTE. The subjects in their study had experienced an ALTE, as defined by having a history of being found blue or pale, not breathing, usually limp, and requiring vigorous shaking or mouth-to-mouth resuscitation before beginning to breathe or arouse. The subjects were between 1 and 4 months of age and were challenged with 5% CO_2 and 15% O_2 during REM and NREM sleep. Sleep state was determined by monitored by EEG's, EOG's, and EMG. Respiration was monitored by thoracic and abdominal strain gauge. Each subject was recorded during a daytime sleep study, with ventilatory response being measured after baseline recordings. During the steady-state hypoxic challenge, periodic breathing and arousal were observed frequently in both groups. Arousal was not defined. Both periodic breathing and arousal occurred more frequently in the control group and was considered by these authors to be an adaptative response. The percent change in

ventilation in response to the hypoxic challenge was quite variable in both groups of subjects but not significantly different between groups. Ventilation increased in response to hypercarbia during REM and NREM sleep in all of the subjects. The mean maximum carbon dioxide sensitivity (increase in ventilation per mm Hg increase in PACO2) was similar during REM and NREM sleep for both groups. These authors concluded that the importance of the response to carbon dioxide and hypoxia in a sleeping infant may be related to arousal and not just to changes in ventilation.

Arousal Response in Infants with Bronchopulmonary Dysplasia (BPD)

Another group of infants who experience an increase in SIDS and in whom frequent episodes of oxygen desaturation have been noted are those with bronchopulmonary dysplasia (BPD) (Werthammer, Brown, Neff, & Taeusch, 1982; Garg, Kurzner, & Bautista, 1987). The arousal response to an inspired oxygen tension of 80 torr was studied in 12 subjects with BPD (Garg, Kurzner, Bautista, & Keens, 1988). The subjects were born prematurely (mean gestational age at birth, 29.2 weeks) and were studied at term (41.4 weeks, postconceptual age). The procedure for inducing a hypoxic response was to rapidly decrease the inspired oxygen tension to 80 torr by blending 100% nitrogen with room air into the oxygenhood. The subjects breathed this gas mixture for 3 minutes or until arousal occurred. If arousal did not occur after 3 minutes, the subject was returned to breathing room air and the hypoxic challenge was repeated after 10 minutes. The hypoxic arousal response was defined as abnormal only if a subject failed to arouse during each

of two consecutive hypoxic challenges. Eleven of the 12 subjects aroused to the hypoxic challenge. The mean oxygen saturation at arousal was 63% (no range given). In the one subject who did not arouse, the hypoxic challenge was only given once, because of prolonged apnea following the first hypoxic challenge. The lowest oxygen saturation for this subject was 63%; the same as the mean for those who did arouse.

Although the arousal response was present, 67% of the subjects had prolonged apnea with bradycardia after the arousal response, and 33% required brief ventilatory assistance with bag and mask to restore a normal breathing pattern. Thus, some of these subjects were not able to maintain a normal breathing pattern following a hypoxic challenge, even though they exhibited an arousal response and a ventilatory response, as evidenced by a decrease in end tidal carbon dioxide. This study is the only one to date to investigate the arousal response to hypoxia in subjects who were born prematurely. They were studied at 12 weeks post birth. In addition to being born prematurely, the subjects had had respiratory distress syndrome and had been treated with supplemental oxygen and/or mechanical ventilation for at least 28 days. However, subjects were not receiving supplemental oxygen at the time of the study, nor were they observed to be having apnea, bradycardia or cyanosis. The subjects were stated to have BPD; however, no criteria were given for making this diagnosis. The mean oxygen saturation at arousal was 63%. This value is somewhat difficult to interpret, because, since these subjects had BPD, one would expect them to have a lower than normal oxygen saturation, but the baseline values were not given. However, since these subjects were not on supplemental oxygen at the time of the study their oxygen saturation was probably 90% or greater.

Relationship between Catecholamines and Hypoxia

A possible linkage between increased catecholamines, apnea and SIDS in some infants has been suggested (Bhat, Scanlon, Lavenstein 1983; Perrin, Becker, Madapallimatum, Curtz, Bryan, & Sole, 1984). Therefore, Rodriquez, Warburton and Keens (1987) studied 15 subjects who had experienced an ALTE, and obtained catecholamine levels from an indwelling catheter before, during and following hypoxic challenges. Hypoxic challenges were performed during quiet sleep only, by blending 100% nitrogen with room air in an oxygenhood until the PIO_2 reached 80 torr (equivalent to breathing 11% oxygen). This PIO_2 was maintained for 3 minutes or until arousal occurred. Four (27%) of the subjects aroused, and 11 (73%) failed to arouse. A comparison of the catecholamine levels between those who aroused and those who failed to arouse revealed: 1) a significantly higher serum epinephrine level and serum norephrine level in those who failed to arouse and 2) no differences in serun dopamine concentrations. The serum epinephrine and norepinephrine levels were greater while awake, during sleep and during the hypoxia challange in those who had an abnormal hypoxic arousal response, compared to those with a normal hypoxic arousal response. The possible explanations for higher catecholamine levels in these subjects are either a primary abnormality in catecholamine secretion or metabolism or an increase due to chronic hypoxia.

The ventilatory response to carbon dioxide in infants deemed to be at risk for SIDS has been the focus of three recent abstracts. A higher incidence of abnormal ventilatory responses was found in subjects with apnea of infancy and in siblings of SIDS than in a group of infants

deemed to be at risk (i.e., prolonged apnea, BPD) (Marotta, Fort, Mondestin, Hiatt & Hegyi, 1984). The technique for measuring ventilatory response to carbon dioxide was a computerized carbon dioxide waveform analyzer that analyzes breath by breath responses. The results of this study however, may be confounded by the wide range of ages of the subjects at the time of the study. For example, the siblings of the SIDS had a mean age of 49 weeks post conceptual age, plus or minus 18 weeks; thus the range was from 31 to 67 weeks. The range of the other two groups was from 40 to 68 weeks (apnea of infancy) and 34 to 54 weeks (risk infants). This same group of researchers, using the same technique of measuring carbon dioxide (and perhaps the same subjects), in another report found that the highest proportion of abnormal carbon dioxide slopes were in subjects with gastroesophageal reflux, apnea of infancy and in siblings of SIDS (Mondestin, Mojica, Anwar, Hiatt, & Hegyi, 1985). The post conceptual age of the subjects at the time of the study also varied greatly, with the mean age ranging from 39 to 60 weeks.

In contrast to the findings of Mondestin, Mojica, Anwar, et. al. (1985), hypercarbic ventilatory responses were found not to be depressed in subjects with ALTE, or siblings of SIDS victims by Coleman, Reardon, Mammel and Boros (1985). In comparing those who developed subsequent apnea with those who did not, those who developed subsequent apnea had lower $PACO_2$ values ($p<.001$) and higher hypercarbic ventilatory response values.

In summary, the differences in all these studies, with some finding a difference in arousal or ventilatory response in risk groups and some not, may be attributed in part to: 1) differences in ages of subjects at

the time of study; 2) criteria for sample selection of individual subjects, for example criteria for what constitutes the diagnosis "apnea of infancy"; 3) standardization or lack thereof in implementing the challanges and the rate at which hypoxia or hypercarbia are produced; 4) sleep state at the time of the measurements; 5) criteria used to determine arousal; 6) the criteria used to determine what constitues an abnormal response, and 7) the length of time between an ALTE event and the time of the study. While these tests may identify "groups" who are at risk, they do not have sufficient specificity or sensitivity to identify individual subjects because of the wide range of interindividual variability.

Table 1

Summary of Selected Data from Arousal Studies: Animals

Author & Year	Subjects	No.	Arousal Criteria	Arousal Stimulus/Findings
Bowes, Woolf, Sullivan & Phillipson 1980	dogs	5	From NREM: abrupt change in EEG & by behavioral changes; From REM: by behavioral criteria.	Effect of sleep fragmentation on arousal responses to respiratory stimulation: 1) oxygen saturation at arousal decreased in both sleep states significantly after sleep framentation; 2) alveolar PCO_2 at arousal increased in both sleep states after sleep fragmentation; 3) mean sleep latency decreased significantly after sleep fragmentation; 4) hypercapnic and hypoxic ventilatory responses unimpaired by sleep fragmentation; (5) arousal response to laryngeal stimulation impaired after sleep fragmentation.
Fewell 1987	newborn lambs	6	Wakefulness: head up, EEG criteria, occasional eye movement, tonic activity, nuchal EMG From NREM: head up, EEG criteria, no eye movements, tonic activity of nuchal EMG; From REM: EEG criteria, REM, no nuchal EMG activity.	Effect of sleep fragmentation on arousal response to UAO*: 1) sleep fragmentation produced statisticaly significant increase in time to arousal & a decrease in oxygen saturation in NREM sleep; 2) no significant changes during REM sleep.

* UAO - upper airway obstruction

Table 1 (cont.)

Summary of Selected Data from Arousal Studies: Animals

Author & Year	Subjects	No.	Arousal Criteria	Arousal Stimulus/Findings
Bowes, Townsend, Bromley, Kozar & Phillipson 1981a	dogs	4	From NREM: abrupt change in EEG & by behavioral changes; From REM: by behavioral criteria.	Effect of carotid body denervation and vagal blockade on arousal response to airway occlusion: 1) intact animals: no significant difference in oxygen saturation at arousal in REM or NREM sleep; 2) bilateral carotid body denervation: Oxygen saturation at arousal decreased significantly from intact values in REM and NREM sleep; 3) bilaterial vagal blockade: no significant differences in oxygen saturation from intact values; tested in NREM sleep only; 4) ventilatory response impaired after carotid body denervation.

Table 1 (cont.)

Summary of Selected Data from Arousal Studies: Animals

Author & Year	Subjects	No.	Arousal Criteria	Arousal Stimulus/Findings
Phillipson Kozar, Rebuck & Murphy 1977	dogs	3	From NREM: abrupt change in EEG & by behavioral changes; From REM: by behavioral criteria.	Arousal and ventilatory response to hyperoxic hypercapnia during sleep: 1) duration of rebreathing before arousal longer and more variable in REM compared to NREM; 2) alveolar CO_2 at point of arousal higher during REM compared to NREM sleep; 3) during NREM, progressive increase in tidal volume and frequency as end tidal CO_2 increased; irregular pattern in response to CO_2 in REM.
Phillipson, Sullivan, Read, Murphy & Kozar 1978	dogs	4	From NREM: EEG & behavioral criteria; From REM: by behavioral criteria.	Ventilatory & waking responses to acute hypoxia with normal alveolar CO_2 during sleep: 1) oxygen saturation decreased in REM to a mean of 70% before arousal, compared to oxygen saturation of 87.5% during NREM sleep with eucapnic $PACO_2$; 2) with $PACO_2$ increased during hypoxia, oxygen saturation at arousal higher in NREM but not during REM sleep; 3) ventilatory response increased in NREM sleep with hypoxia & elevated $PACO_2$; 4) ventilatory response to eucapnic hypoxia

Table 1 (cont.)

Summary of Selected Data from Arousal Studies: Animals

Author & Year	Subjects	No.	Arousal Criteria	Arousal Stimulus/Findings
Fewell & Baker 1987	lambs	8	From NREM: point of arousal determined by a change in ECG from high voltage slow wave pattern to a low voltage fast wave pattern; From REM: point of arousal determined by return of tonic activity from nuchal electro-myogram.	Arousal response to breathing 10%, 5% or 0% oxygen: 1) rate of oxygen desaturation with 10%, 5%, or 0% oxygen not affected by sleep state; 2) oxygen saturation at arousal to rapidly developing hypoxemia was affected by sleep state; NREM sleep arousal occurred @ similar oxygen saturation despite the different rates of oxygen desaturation that occurred when the lambs were breathing different oxygen mixtures; in active sleep, arousal occurred @ different oxygen saturation with different oxygen concentrations suggesting that arousal was dependent on the rate of change of oxygenation; 3) electrocortical signs of cerebral hypoxia & primary apnea at times preceded arousal from sleep.

Table 1 (cont.)

Summary of Selected Data from Arousal Studies: Animals

Author & Year	Subjects	No.	Arousal Criteria	Arousal Stimulus/Findings
Fewell & Konduri 1988	newborn lambs	12	From NREM: point of arousal determined by a change in ECG from high voltage slow wave pattern to a low voltage fast wave pattern; From REM: point of arousal determined by return of tonic activity from nuchal electro-myogram.	Repeated exposure to rapidly developing hypoxemia influenced interaction between oxygen & carbon dioxide in causing arousal from sleep: 1) repeated exposure to hypoxemia influenced the arousal response in both NREM & REM sleep; there was increase time to arousal & decreased saturation at arousal; 2) repeated exposure to hypoxemia indicated evidence for an interaction between oxygen and carbon dioxide in initiating arousal from both sleep states; the time to arousal decreased & the saturation at arousal increased as increasing amounts of carbon dioxide were added to the hypoxic gas mixture.
Fewell, Williams, Szabo & Taylor 1988	newborn lambs	5	From NREM: point of arousal determined by a change in ECG from high voltage slow wave pattern to a low voltage fast wave pattern; From REM: point of arousal determined by return of tonic activity from nuchal electro-myogram	Effect of repeated induced UAO* on the arousal and cardiopulmonary response: 1) arousal occurred from both sleep states during UAO, but was delayed during REM compared to NREM; 2) time to arousal was increased and oxygen saturation at arousal decreased by repeated UAO during REM sleep; 3) heart rate decreased during UAO

Table 1 (cont.)

Summary of Selected Data from Arousal Studies: Adults

Author & Year	Subjects	No.	Arousal Criteria	Arousal Stimulus/Findings
Berthon-Jones & Sullivan 1982	adults (normal)	9	From NREM: desynchronzation & return of tonic EMG; From REM: return of tonic EMG; Wakefulness: behavioral criteria, EEG criteria.	Effect of eucapnic hypoxia during sleep; 1) failure to arouse by 70% oxygen saturation in nearly half tests performed during NREM and REM sleep.
Berthon-Jones & Sullivan 1984	adults (normal)	13	Arousal not defined. Sleep stages monitored by EEG, EMG, EOG, & observations of body & eye movements. Tests continued until obvious behavioral arousal.	Effect of sleep state on ventilatory & arousal responses to induced hypercapnia; 1) arousal threshold increased with deepening NREM sleep, and decreased in REM sleep in males; males aroused at increasing alveolar PCO_2; 2) in REM alveolar PCO_2 at arousal lower than in stages 3 & 4 NREM in males; 3) females showed no significant changes in alveolar PCO_2 arousal threshold in REM or NREM.
		13		
Issa & Sullivan 1982	adults (normals)		From NREM: EEG, EMG changes From REM: EMG changes.	Arousal response to total airway occlusion: 1) Occlusion induced arousal in all subjects; 2) in NREM sleep the duration of time prior to arousal was longer & more variable than in REM sleep.

Table 1 (cont.)

Summary of Selected Data from Arousal Studies: Adults

Author & Year	Subjects	No.	Arousal Criteria	Arousal Stimulus/Findings
Sullivan & Issa 1980	adults (sleep apnea)	5	not stated; EEG, EMG, REM monitored;	Arousal mechanisms in obstructive apnea: 1) duration of apnea longer and oxygen saturation lower in REM compared to NREM sleep; 2) increased EMG activity consistently present prior to relief of occlusion; 3) arousal threshold elevated during REM compared to NREM.

Table 1 (cont.)

Summary of Selected Data from Arousal Studies: Infants

Author & Year	Subjects & Mean age	No.	Arousal Criteria	Arousal Stimulus/Findings
McCullock, Brouillette, Guzzetta & Hunt 1982	infants (7.3 weeks) (9.3 weeks)	22 (control) 11 (NMSIDS)* (AOI)*	eye opening & crying	Hypercarbic and hypoxic arousal response; 1) hypercarbic arousal threshold was significantly higher in AOI subjects than in controls; 2) an arousal response to hypoxia occurred in 70% controls, but in 9% of NMSIDS.
van der Hal, Sargent, Platzker, & Keens 1982	infants (10.9 months) (4.1 months)	6 (control) 15 (NMSIDS) (AOI)	restlessness, agitation, eye opening	Hypercarbic and hypoxic arousal response; 1) pressure of inspired carbon dioxide significantly greater at arousal in NMSIDS than in control; 2) all controls aroused to hypoxia; 60% of NMSIDS failed to arouse to hypoxia.
Ariago, Nagel & Guilleminalt 1980	infants (2.7 months) (2.2 months)	5 (control) 9 (AOI)	EEG, EOG, EMG changes; no criteria for arousal given.	Arousal & ventilatory response during REM & NREM: 1) with 15% O_2, periodic breathing & arousal observed more frequently in controls; ventilatory response to 15% O_2 not different in 2 groups; 2) ventilatory response to hypercarbia present during REM & NREM in both groups; mean maximum CO_2 sensitivity similar during REM & NREM for both

* NMSIDS = near miss sudden infant death syndrome

Table 1 (cont.)

Summary of Selected Data from Arousal Studies: Infants

Author & Year	Subjects & Mean age	No.	Arousal Criteria	Arousal Stimulus/Findings
Rodriquez, Warburton, & Keens 1987	infants (5.5 month) (median)	15 AOI*	From NREM only: agitation, body movement, eye opening, crying & EOG changes;	Arousal response to inspired oxygen of 80 torr: 1) 73% didn't arouse to hypoxia; 2) serum epinephrine and norepinephrine levels significantly greater in those with abnormal hypoxic arousal response compared to those with normal hypoxic arousal response; 3) no difference in serum dopamine concentrations between those with normal/abnormal hypoxic arousal response.
Garg, Kurzner, Bautista, & Keens 1988	infants with BPD* (41.4 weeks, PCA)	12	From NREM only: agitation, body movement, eye opening & crying.	Arousal response to hypoxia: 1) 92% aroused normally; however 67% experienced prolonged apnea with bradycardia & 33% required brief ventilatory assistance to restore normal breathing, after the arousal response; 2) mean oxygen saturation at arousal was 63%.

* AOI = Apnea of infancy
* BPD = Bronchopulmonary Dysplasia
* PCA = Post conceptual age

Table 1 (cont.)

Summary of Selected Data from Arousal Studies: Infants

Author & Year	Subjects & Mean age	No.	Arousal Criteria	Arousal Stimulus/Findings
Marotta, Fort, Mondestin Hiatt & Hegyi 1984	infants 44 wks 54 wks 49 wks	 49 11 6	Not stated.	Ventilatory response to carbon dioxide: 1) near miss and siblings of SIDS had more blunted response to carbon dioxide than group identified as being at risk.
Mondestin, Mojica, Anwar, Hiatt, & Hegyi 1985	infants 49 wks 60 wks 41 wks 41 wks 47 wks 49 wks 43 wks 39 wks	126 (7) (19) (21) (43) (18) (8) (5) (5)	Not stated.	Ventilatory response to carbon dioxide: 1) the highest proportion of abnormal slopes were in the reflux, AOI* and SSIDS* groups.
Coleman, Reardon, Mammel, & Boros 1985	infants no ages given	174 (65) (78) (31)	Not stated.	Hypercarbic ventilatory responses (HVR): 1) HVR values similiar in the 3 groups; 2) resting $PACO_2$ values were lower in AOI group; 3) those who developed subsequent apnea had higher HVR values and lower $PACO_2$ values than those who did not.

* AOI = apnea of infancy

* SSIDS = siblings of SIDS

CHAPTER IV

METHODOLOGY

Subjects

The subjects consisted of a convenience sample of eleven premature newborns from a large university-based teaching hospital with a tertiary level nursery. Subjects meeting the following criteria participated in the study:

1) birth weight equal to or less than 2000 grams;
2) gestational age of less than 37 weeks at the time of birth;
3) breathing spontaneously;
4) receiving not more than 23-25% inspired oxygen at the time of the study and
5) absence of neurological disorders affecting control of breathing (e.g., spina bifida, seizures disorders); absence of cranio-facial anomalies; and absence of grade III or IV intraventricular hemorrhage.

This study was approved by the Committee on Human Research, University of California, San Francisco. Informed consent was obtained from the parent(s) prior to the subjects being accepted into the study. Parent(s) could be present for any or all of the study and could participate in any care giving activities as they would normally do in the special care nursery.

Procedure

Subjects were studied during sleep following a regular scheduled feeding. Studies were conducted between 9 A.M. and 6 P.M. in the Pediatric Pulmonary Laboratory, in a quiet, darkened room designated and equipped for neonatal and infant sleep studies. The ambient room temperature was maintained between 25-26 degrees Centigrade. The subjects were brought to the Pediatric Pulmonary sleep lab in an open crib with a transport heart rate and respiratory rate monitor attached. In the sleep lab the transport heart rate and respiratory monitor was removed and the following variables were monitored non-invasively and recorded continuously on an 8 Channel Grass R (model 78D, Quincy, MA) polygraph: 1) heart rate and rhythm by a 3 lead electrocardiogram (ECG), 2) respiratory rate and pattern by thoracic and abdominal mercury in rubber strain gauges, 3) oxygen saturation by pulse oximetry (Nellcor N100, Nellcor, Hayward, CA), 4) skin surface oxygen and carbon dioxide tension by an oxygen and carbon dioxide electrode (Novametrix, model 809A and 810A, respectively, Wallingford, Ct.) with the electrodes heated to 43.5 and 43 degrees Centigrade, respectively, 5) respired carbon dioxide by a prenasal catheter attached to a respired carbon dioxide monitor (Puritan Bennett, Model 223) with a sampling rate of 50cc per minute and a response time for 10 to 90% of 0.4 second, and 6) changes in intrathoracic pressure were measured with a saline filled 5 French feeding catheter in the lower one-third of the esophagus. Correct placement of the catheter was confirmed by first advancing the catheter into the stomach and then slowly withdrawing it. A distinctive

change in the waveform pattern occurred as the catheter moved into the esophagus.

The use of pulse oximetry provides a reliable measure (r=.9) of oxygen saturation in prematures (Jennis & Peabody, 1987). Skin surface oxygen and carbon dioxide tension are reliable measures of arterial oxygen and carbon dioxide tension in prematures (Deckardt & Steward, 1984; Lofgren & Andersson, 1983; Monaco & Quitty, 1981; Laptook & Oh, 1981).

Following application of the monitoring devices, the subjects were fully dressed, fed, swaddled in a blanket and placed in either a prone or side-lying position in an open crib. Subjects were studied twice; initially just prior to hospital discharge and a second time when the subjects were between 12-16 weeks postnatal age. Each study took approximately 4-5 hours, including time to apply the electrodes and recording devices, feeding time and awake time that may have occurred during the study. The length of each actual recording period during sleep was approximately 3 hours. All recordings were obtained at a paper speed of 3mm/second.

Prior to each study the skin surface oxygen and carbon dioxide electrodes were remembraned and were calibrated with low (0 torr oxygen and 23 torr carbon dioxide) and high (91 torr oxygen and 47 torr carbon dioxide) calibration gases. The respired carbon dioxide monitor was calibrated with 0% (room air) and 2, 4, and 6% carbon dioxide before each study, with the resultant waveform calibrated to and displayed on the polygraph tracing, such that a 1 torr change in respired carbon dioxide was reflected by a 1mm change on the tracing. The polygraph channel used for monitoring intrathoracic pressure was calibrated

before each study so that a change of 1 cm water pressure was reflected by a 1mm change on the polygraph tracing. The oxygen saturation monitor has an automatic internal calibration process that occurs each time the machine is turned on. The output was calibrated with the Grass R polygraph, such that a 1 percent change in oxygen saturation was reflected by a 1mm change on the polygraph tracing.

The subjects were placed prone or in a side-lying position in an open crib under an oxygenhood. During the course of the study the subjects breathed three different gas mixtures sequentially. At the beginning of the study the variables were recorded during a period of baseline sleep ranging from 51 to 89 minutes (mean 66 minutes) while the subjects breathed 21% oxygen. With the subject in a stable sleep state, (consistent REM or NREM), the gas composition was changed from 21% oxygen to 17% oxygen for 15 minutes, or until arousal occurred, or until an oxygen saturation of 75% was reached. Before initiating the hypoxic challenge, the subject was in a stable sleep state for a minimum of two minutes. At the end of the hypoxic challenge, the inspired gas composition was returned to 21% oxygen. The criterion for initiating the hypercarbic challenge following the hypoxic challenge was that the subject be in a stable sleep state and that the recorded variables had returned to baseline values. Before initiating the hypercarbic challenge, the subject was in a stable, consistent sleep state for a minimum of three minutes. The hypercarbic challenge consisted of 2, 4, or 6% carbon dioxide and 21% oxygen given sequentially for 6 minutes each or until arousal occurred. At the end of the hypercarbic challenge the subject was returned to breathing room air and the study was ended. The hypercarbic challenge was always given after the hypoxic

challenge, since there is no evidence in the literature to support that the order of the treatments would make any difference in response to the treatments.

All gases were warmed to 26-27 degrees Centigrade and delivered at a flow of 10 L/minute when the small oxygenhood (6.5 liters, volume) was used at the earlier postnatal age and at a flow of 15L/minute when the larger oxygenhood (11.5 liters, volume) was used at the later postnatal age. To ensure that the flow of the gas mixtures into the oxygenhood did not flow directly on the subject's head, which might cause a tactile stimulus for arousal, all subjects wore a knitted cap on their head throughout the duration of the studies. All manipulations required for changing the concentration of inspired gases was done without touching the subject, the crib or the oxygenhood and without any auditory stimulation. The liter flow of gases into the oxygenhood was the same during baseline and the challenges for any given study.

An oxygen analyzer (Beckman Instruments, Inc., Fullerton, CA) was placed inside the oxygenhood to verify that the ambient oxygen inside the oxygenhood was 17% during the hypoxic challenge. During the hypercarbic challenge, an increase in the baseline recording of the inspired carbon dioxide on the polygraph tracing served to verify that with each increase in ambient carbon dioxide, there was a corresponding increase in the inspired concentration. The beginning and ending of each challenge and the point of arousal, if any, was marked on the polygraph tracing at the time of occurrence. The following variables were recorded on the polygraph tracing by the investigator every 50 seconds: oxygen saturation, pulse rate from the oximeter, skin surface oxygen and carbon dioxide, the respired carbon dioxide value and the

subject's state (i.e., REM, NREM, awake, arousal, awake or indeterminate). The subject's state was determined according to the definitions given in Chapter I. Respiration was not used as a criterion for sleep state as has been recommended (Rigatto, Kalapezi, Leahy, 1980). The subjects were observed for state continuously throughout the study by the investigator. In previous work, the investigator achieved an interrater reliability score of .85 or higher in assigning sleep states to premature newborns using the same criteria used in this study. Each sleep state was given a code number, and that number was recorded after determining the subject's state at the end of each 50 seconds during the sleep study. Each arousal response, whether occurring spontaneously, or in response to external events (e.g., noise or touching the subject to manipulate recording devices) or in response to the respiratory events under study was recorded on the polygraph tracing at the time of its occurrence.

Data Extraction

The following criteria were used to extract data from each sleep record. For baseline measures, the transcutaneous oxygen and carbon dioxide electrodes had to be on the subject for a minimum of 15 minutes for stabilization of the electrodes and the subject had to be in a stable sleep state. The value of each monitored variable was extracted at the same point in time from the tracing throughout the period of baseline sleep.

To assess the responses to the hypoxic challenge, the value of each monitored variable was extracted at the same point in time from the

tracing just prior to initiation of the hypoxic challenge and again 1) at the end of the hypoxic challenge, or 2) just prior to arousal, or 3) when the oxygen saturation decreased to less than the pre-determined criteria for ending the hypoxic challenge.

To assess the responses to the hypercarbic challenge, the value of each monitored variable was extracted at the same point in time from the tracing just prior to initiation of the hypercarbic challenge and again 1) at the end of each sequential increase in carbon dioxide, and 2) just prior to arousal.

The number of apneas of at least 6 seconds duration occurring during the sleep study were counted and categorized as to type (central, obstructive or mixed) by the investigator. Each apneic episode was then reviewed by a member of the dissertation committee (WHT) and 100% agreement was reached as to type of apnea. For each apnea, the following variables were extracted from the sleep record: oxygen saturation prior to apnea and the lowest oxygen saturation reached, heart rate before and during apnea, sleep state prior to and following the apnea, and whether the apnea was terminated by arousal. For the apnea to be considered to be terminated by arousal, the arousal response had to interrupt the apnea and be evident before spontaneous breathing was initiated. The duration of apnea during the first month of life in one group of prematures showed a modal distribution for central apneas of about 8 seconds (Lee, Caces, Kwiatkowski, Cates, & Rigatto, 1987). Since the arousal response to apnea in prematures had not been previously investigated, a minimum apnea duration of 6 seconds was selected in order to provide a wide range of apnea durations over which

to study the arousal response and yet not include respiratory pauses as short as 3-4-5 seconds in duration.

Sleep state was counted as the number of minutes spent in REM or NREM during baseline, during the hypoxic challenge and during the hypercarbic challenge. The number of spontaneous behavioral arousals occurring during the baseline were counted, as well as whether or not behavioral arousal occurred in response to the hypoxic and hypercarbic challenge. An arousal response was defined behaviorally (see Chapter I), but was also evident on the polygraph tracing by an increase in magnitude from baseline of the respiratory pattern as recorded by the mercury and rubber strain gauges around the chest and abdomen and by the increase from baseline of the intrathoracic pressure tracing. The ending of an arousal response could likewise be identified behaviorally, but also by a return of these variables to baseline levels.

Examples of selected pages from sleep recordings are given in Appendices B-J. Examples shown are from the baseline, during the hypoxic challenge and during the hypercarbic challenge. Examples of an apnea terminated by arousal and one not terminated by an arousal response are given in Appendices K-L.

Data analysis was performed that produced descriptive statistics and statistical tests of the following relationships:

1. condition under which apnea occurred (baseline or hypoxic challenge and a) lowest oxygen saturations, b) duration of apnea, and c) beginning oxygen saturation (Mann Whitney U);
2. condition under which apnea occurred (baseline or hypoxic challenge) and a) arousal response, and b) type of apnea (Chi square test);

3. arousal/non-arousal response to apnea by type of apnea (Chi square test);
4. lowest oxygen saturation during apnea by type of apnea (Mann-Whitney U);
5. lowest oxygen saturation during apnea by duration of apnea (Spearman's rho);
6. arousal/non-arousal response to apnea by duration of apnea (Mann Whitney U);
7. arousal response to apnea by 3 predictor variables (logistic regression);
8. rate of spontaneous arousals during baseline sleep by both postnatal age and sleep state (repeated measures analysis of variance);
9. arousal response to hypoxic and hypercarbic challenges by postnatal age (matched pairs sign test);
10. oxygen saturation (for total group) in response to hypoxic challenge by postnatal age (matched pair signed rank test);
11. oxygen saturation at arousal (arousers) to hypoxic challenge by postnatal age (Mann Whitney U);
12. oxygen saturation at end of hypoxic challenge (non-arousers) by postnatal age (Mann Whitney U);
13. oxygen saturation for arousers/non-arousers by early postnatal age (Mann Whitney U);
14. oxygen saturation for arousers/non-arousers by later postnatal age (Mann Whitney U);

15. carbon dioxide tension (for total group) in response to hypercarbic challenge by postnatal age (matched pair signed rank test); and
16. carbon dioxide tension for arousers/non-arousers by later postnatal age (Mann Whitney U).

Non-parametric tests of statistical significance used in this data analysis were the Mann Whitney U, Spearman's rho, and the Chi square. These tests do not assume a normal distribution of the data and were, therefore, the most appropriate to use. The matched pairs sign test, a non-parametric analog for the matched pair t-test, was used to test for statistical significance of the arousal response to both challenges for those 8 subjects who were studied at both an early and a later age; each subject was compared to himself to answer the question: Were there significantly more arousals to the challenges at the early versus the late postnatal age. The matched pairs signed test was also used to compare the oxygen saturation values by postnatal age, during the hypoxic challenge and to compare the transcutaneous carbon dioxide values by postnatal age during the hypercarbic challenge.

A repeated measures analysis of variance (with two within subject factors) was used to test if there was a difference between early versus later postnatal age and between REM and NREM sleep in the rate of spontaneous arousals during baseline sleep for those 8 subjects who were studied at two points in time.

The logistic regression is similar to multiple regression and is used when the dependent variable is dichotomous. The goal is to predict this dichotomous outcome variable. The three predictors are entered into the model simultaneously. Thus the relationship of each of the

three predictors with the dependent variable is adjusted for the remaining two. The criterion for statistical significance was set at $p<0.05$.

CHAPTER V

RESULTS OF THE STUDY

The findings of this study are discussed in 5 sections; a description of the sample is followed by the presentation of results in relation to each of the 4 hypotheses. A summary of the statistical findings is presented in Table 6 at the end of the chapter.

Description of the Sample

Characteristics of the subjects are shown in Table 2. The mean gestational age at birth was 30 weeks (range 27 to 32 weeks) and the mean birth weight was 1238 grams (range 820 to 1460). The median postnatal age of the subjects at the time of the first sleep study was 7 weeks (4-12, range), with a median postconceptual age of 37 weeks (35-43, range). At the second sleep study, the median postnatal age of the subjects was 14.5 weeks (10-16, range) with a median postconceptual age of 44 weeks (40-45, range). No subject was receiving supplemental oxygen at the time of the studies. Eleven subjects were studied at the early postnatal age and of these, eight returned for a follow-up study at a later postnatal age. Failure to return for a follow-up study was due to unexpected relocation of the family out of state (1) and a change of mind about returning for the repeat study (2). Two subjects received chloral hydrate (50mg/kg) to initiate and maintain sleep. Chloral hydrate has been shown not to have any significant effects on hypercarbic or hypoxic sensitivity in animals (Hunt, Hazinski & Gora,

Table 2

Characteristics of Subjects

Subject	Gender	Birth weight (grams)	Gestational Age (weeks)	APGAR	Medical Diagnoses	Postnatal age/ Postconceptual Age (weeks) Sleep study # 1	Postnatal age/ Postconceptual Age (weeks) Sleep study # 2	Home on Monitor
1	fe	900	27	3 & 6	RSD;* PDA;* Hyperbilirubinemia; history of apnea & bradycardia, associated with feedings	11 / 38	16 / 43	No
2	m	1720	31	6 & 4	RDS; PDA; Hyperbilinubiremia, Hypertrophic cardiomyopathy, resolving; history of apnea & bradycardia.	5 / 36	10 / 41	Yes
3	fe	1360	30	7 & 7	Transient RDS; PDA, Hyperbilirubinemia history of apnea & bradycardia	6 / 36	15 / 45	No

* RDS - Respiratory Distress Syndrome; PDA - Patent Ductus Arteriosus

Data for Hypoxic Challenge from Subjects 1, 3, 4, 5, 6, 8, and 9.

Data for Hypercarbic Challenge from Subjects 1, 2, 3, 4, 5, 6, 8, and 9.

Table 2 (cont.)

Characteristics of Subjects

Subject	Gender	Birth weight (grams)	Gestational Age (weeks)	APGAR	Medical Diagnoses	Postnatal age/ Postconceptual Age (weeks) Sleep study # 1	Postnatal age/ Postconceptual Age (weeks) Sleep study # 2	Home on Monitor
4	fe	1060	28	1 & 5	RDS; Hyperbilirubinemia history of apnea's bradycardias associated with feedings	7 / 35	12 / 40	Yes
5	fe	1340	30	7 & 9	Transient retained fetal lung fluid; PDA, Hyperbilirubinemia; grade II IVH; history of apnea & bradycardia;	7 / 37	15 / 45	No
6	m	1130	30	2 & 9	Transient RDS; NEC, resolved medically; PDA; hyperbilirubinemia; mild apnea, bradycardia;	8 / 38	15 / 45	No
7	m	820	31	1 & 2	Transient RDS; hyperbilirubinemia; history apnea & bradycardia; bilateral ing. herniorrhaphy; (after sleep study)	12 / 43	N / A	Yes

IVH = Intraventricular hemorrhage
N/A - Not available
NEC = Necrotizing entercolitis

Table 2 (cont.)

Characteristics of Subjects

Subject	Gender	Birth weight (grams)	Gestational Age (weeks)	APGAR	Medical Diagnoses	Postnatal age/ Postconceptual Age (weeks) Sleep study # 1	Postnatal age/ Postconceptual Age (weeks) Sleep study # 2	Home on Monitor
8	fe	1100	29	4 & 6	RDS; hyperbilirubinemia;	7 / 36	13 / 42	Yes
9	m	1460	31	5 & 9	RDS; Seizures, first few days of life; resolved; grade I, IVH, resolved; thrombocytopenia; staph. aureus of umbilicus;	6 / 37	14 / 45	Yes
10	m	1390	31	4 & 7	Transient respiratory distress; Grade I IVH, resolved; Hyperbilirubinemia	4 / 35	N / A	No
11	m	1340	32	7 & 10	PDA; VSD; hypospadias; bilateral herniorrhaphy; (after sleep study)	7 / 39	N / A	Yes

1982) or to affect carbon dioxide chemoreceptor response or sleep states in infants (Lees, Olsen, & McGilliard, 1982).

In the present study, one subject receiving chloral hydrate aroused to 17% oxygen, but not to the carbon dioxide challenge; however, this was at the later postnatal age, when frequency of arousal to both challenges was decreased for all subjects. The other subject received chloral hydrate at the earlier postnatal age and did not arouse to either challenge and was the only subject not to arouse to one of the challenges at the earlier postnatal age. However, this same subject had four apneic episodes with arousal occurring with three of them. One subject was receiving theophylline at the time of both sleep studies. In prematures, theophylline is known to reduce the frequency of apnea (Shannon, Gotay, Stein, Rogers, Todres, & Moylan, 1975; Peabody, Neese, Lucey, Phillip, & Soyka, 1977). In addition, theophylline in prematures increases ventilation, increases ventilatory response to carbon dioxide, regularizes breathing, and improves blood gases (Davi, Sankaran, Simons, Simons, Seshia, & Rigatto 1978). Recent work by Muttitt, Finer, Tierney and Rossman (1988) showed theophylline did not affect apnea duration or oxygen saturation in prematures; however, it significantly reduced the heart rate decrease that accompanied central and mixed apneas.

In the present study, one subject was on theophylline at the time of both sleep studies and had apneas during each sleep study. During the sleep study at the earlier postnatal age, three apneas occurred during baseline sleep without arousal; arousal occurred in association with one apnea during the hypoxic challenge. During the later postnatal age, two apneas occurred in association with the hypoxic challenge; arousal occurred in association with one of the apneic episodes when

oxygen saturation decreased precipitously to 68%. The longest apneic duration was 14-15 seconds and occurred once at each study time. This subject aroused to both challenges at the early postnatal age, and to the hypoxic challenge at the later postnatal age. The effect of chloral hydrate or theophylline on arousal response has not been reported.

Apnea and Arousal

Hypothesis 1. Apnea in prematures is terminated by an arousal response.

During the sleep studies, 42 apneas from 9 different subjects were documented. Seven of these episodes occurred during feedings and were excluded from this analysis because: 1) the variable of interest was arousal from sleep in response to apnea and feedings are presumed to occur in an awake state; 2) a decrease in ventilation during nipple feedings in prematures has been documented (Shivpuri, Martin, Carlo, & Fanaroff, 1983), and respiratory pauses associated with feedings may represent different mechanisms and a sub-category of apnea than those occurring during sleep. Another apnea was excluded due to an incomplete data set for that event, leaving 34 apneas for analysis. These 34 apneas were from the same 9 subjects that had the 42 apneas. The median number of apneas per subject was 2, with a range from 2-9. The length of each sleep study during which these apneas were recorded was approximately 3 hours.

Seven of these apneas occurred during the hypoxic challenge with the remaining 27 occurring during baseline sleep. There was no statistically significant difference between the condition under which

apnea occurred (i.e., baseline or hypoxic challenge) by lowest oxygen saturation ($p = 0.56$), by duration of apnea ($p = 0.43$), by arousal response ($p = 0.88$), or by type of apnea ($p = 0.88$). Only 2 of the 7 apneas that occurred during the hypoxic challenge were terminated by arousal. There was a statistically significant difference between condition under which apnea occurred and beginning oxygen saturation (baseline mean = 96 torr, versus hypoxic challenge mean = 94 torr, $p = .049$). However, this difference of 2 torr in oxygen saturation was deemed not to be biologically significant. In addition, beginning oxygen saturation was not used in any other analysis. Therefore, for further analysis the apneas were grouped together.

Of these 34 apneas, 26 (76%) were central, 6 (18%) were obstructive and 2 (6%) were mixed. For data analysis regarding type of apnea, mixed and obstructive apneas were combined, since by definition a mixed apnea has an obstructive component at the end of the episode, and apnea termination was the variable of interest. The duration of apneas ranged from 6 to 24 seconds. The frequency of arousal/non-arousal response by type of apnea was not statistically significant (Chi square test; $p = 0.47$) (see Figure 3). The lowest oxygen saturation reached during apnea was not significantly different by type of apnea (mean = 81.7%, obstructive versus 83.7%, central; Mann Whitney U, $p = 0.17$). An apneic episode was terminated by an arousal response in 14 out of 34 (41%) events; by comparison, an arousal response did not occur in 20 out of 34 (59%) apneas. In those apneas not terminated by arousal, breathing resumed spontaneously and no subject required any intervention to resolve the apnea or to normalize an irregular or periodic breathing pattern. The relationships among oxygen saturation, duration of apnea

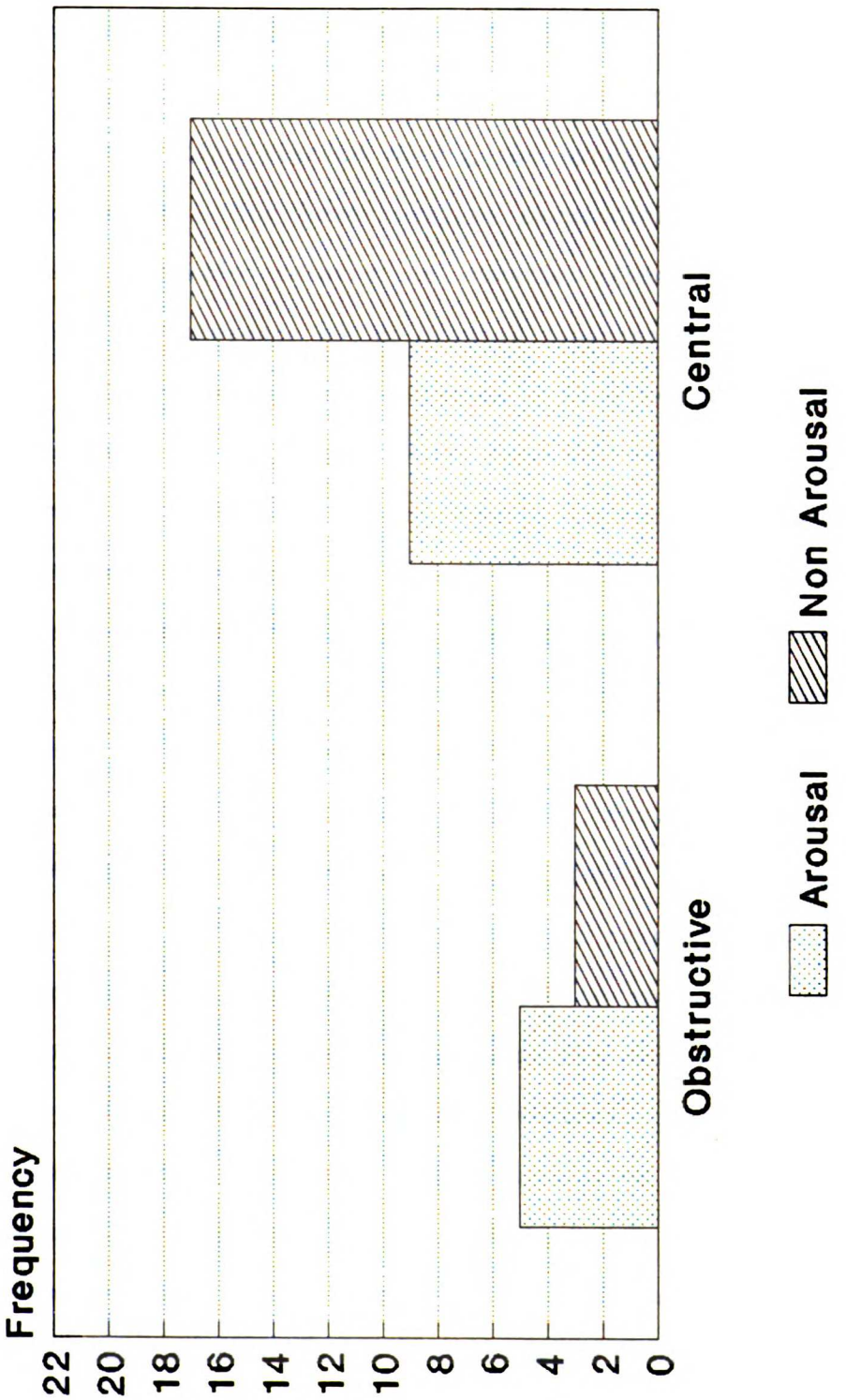


Figure 3. Arousal response by type of apnea (n=34).

and arousal/non arousal response for apneas occurring during baseline and during the hypoxic challenge are shown in Figure 4. The oxygen saturation at arousal for those who aroused, ranged from 68-89%, with a median of 84.5%. For those who did not arouse to apnea, the lowest oxygen saturation reached during the apnea ranged from 68-90%, with a median of 85%. The lowest oxygen saturation reached during apnea was not significantly related to duration (Spearman's rho, $p = 0.25$); however, the presence of an arousal response was significantly related to duration of apnea (mean duration = 12.6 versus 9.1 seconds, arousers versus nonarousers, respectively; Mann Whitney U, $p = 0.031$). The range of apnea duration for those events terminated by arousal was 7-24 seconds compared to 6-15 seconds for those events not terminated by arousal. Thus the data do not support, in general, the hypothesis that apnea in prematures is terminated by an arousal response, being observed in only 41% of the events in this group of prematures at 7 weeks (median) postnatal age (37 weeks, median, postconceptual age).

An arousal response was significantly related to duration, but duration was not significantly related to oxygen saturation. To further define what variables might be related to arousal, a logistic analysis was performed with arousal response as the dependent variable, and heart rate (calculated % change from baseline), rate of change of oxygen saturation (from baseline oxygen saturation prior to apnea onset to lowest oxygen saturation divided by time to reach lowest oxygen saturation) and lowest oxygen saturation reached during the apnea, as predictors. None of these predictors were found to be statistically significant for the entire model ($p = .18$).

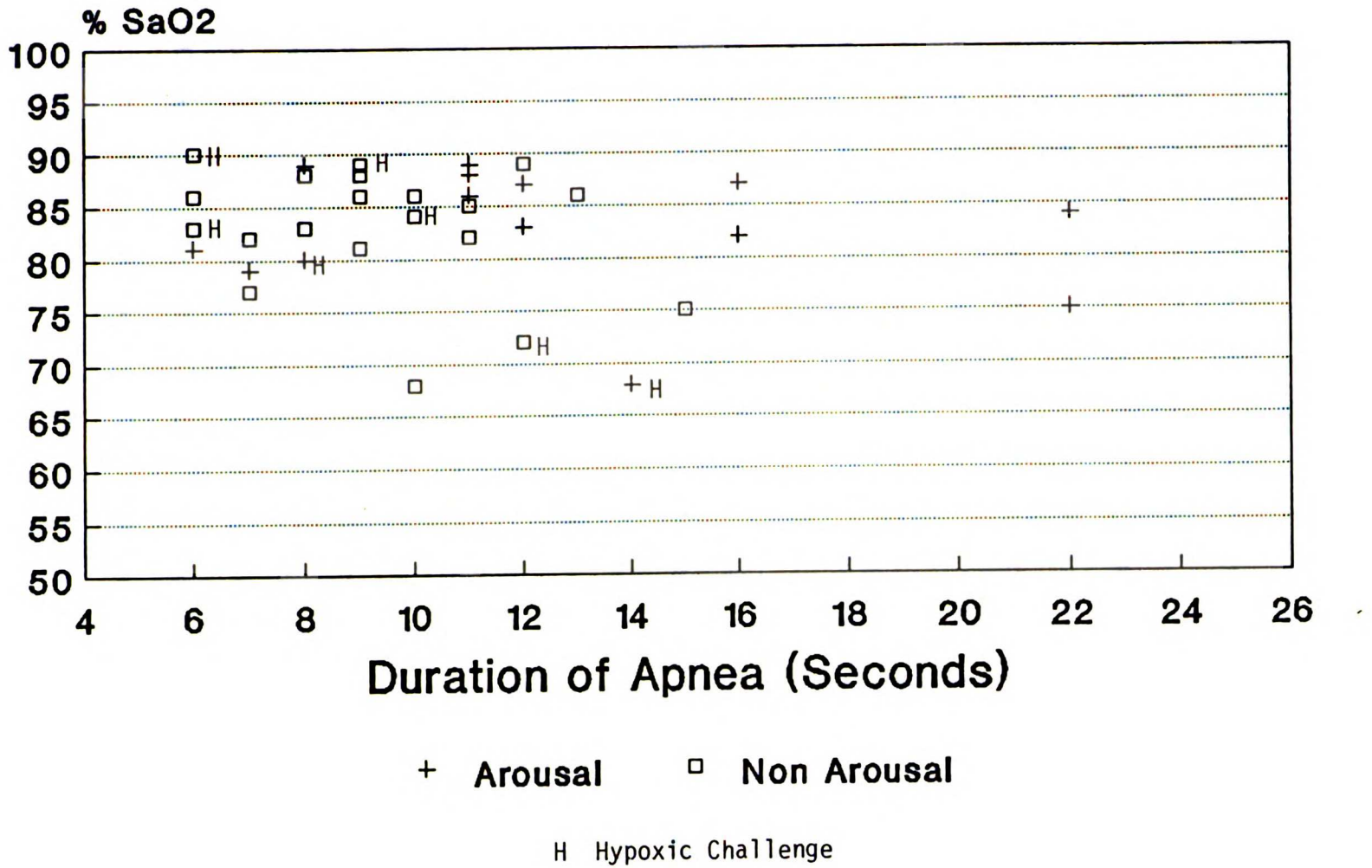


Figure 4. Oxygen saturation, duration of apnea, and arousal response (n=34).

Postnatal Age and Arousal Response

Hypothesis 2. The frequency of arousals occurring spontaneously or in response to respiratory events (hypoxic and hypercarbic challenges) will increase with increasing postnatal age.

The data for this analysis was done only on the 8 subjects who had sleep studies done at both an early and later postnatal age. This permitted analysis of the data by repeated measures analysis of variance and matched pairs sign test. There was no overlap in the ages by either postnatal age (range = 5-11 weeks for early age and 12-16 weeks for later age) or of postconceptual age (range = 35-38 weeks early and 40-45 weeks for later age).

To evaluate whether there was a relationship between the rate of spontaneous arousals per minute during baseline sleep, postnatal age and sleep state, a repeated measures analysis of variance was performed with no grouping factors (i.e., no between subject factors) and 2 trial factors (within subject), postnatal age and sleep state. The rate of spontaneous arousals per minute occurring during baseline sleep was significantly greater at the earlier postnatal age compared to the later postnatal age (overall mean = .205 versus .116 arousals per minute respectively; $F = 16.31$, df 1&7, $p = .005$). The rate of spontaneous arousals occurring during baseline sleep was also significantly different by sleep state, with a higher rate of spontaneous arousals occurring during REM compared to NREM sleep (overall mean = .252 versus .069 arousals per minute respectively; $F = 37.45$, df 1&7, $p = <.001$). The statistical interaction of sleep state by age, was non-significant; thus, these results for the 2 within subjects factors, age and sleep

state, are directly interpretable. Hence, this evidence does not support the hypothesis that the rate of spontaneous arousals during baseline sleep increases with increasing postnatal age. Dichotomous responses of arousal/non-arousal on the same subjects were compared at the earlier and later postnatal ages in response to hypoxic and hypercarbic challenges by matched paired sign test. There was no significant differences in arousal/non-arousal to hypoxic or hypercarbic challenges by postnatal age. Thus, there is lack of evidence from these data to support the hypothesis that the frequency of arousals in response to hypoxia or hypercarbic challenges increases with increasing postnatal age.

To determine if the subjects who aroused to the hypoxic challenge were the same subjects who aroused to the hypercarbic challenge, individual subjects arousal responses at each postnatal age studied were examined (see Table 3). The data suggests that subjects tended to respond the same way (i.e., yes, yes, or no, no) to different respiratory stimuli, and this response appears to be driven by postnatal age. The highest yes-yes responses were at the earlier age (5 of 6) and the highest no-no responses were at the later age (4 of 5).

Hypoxic Challenge and Arousal Response

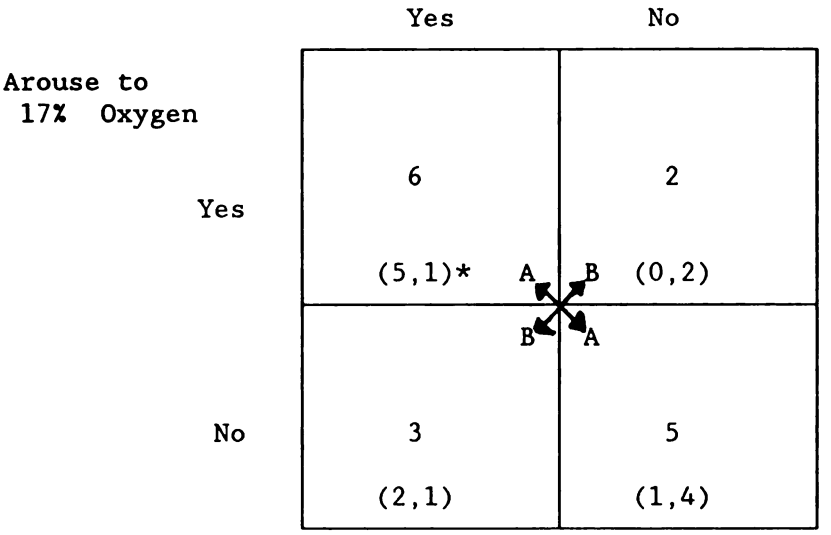
Hypotheses 3. Arousal threshold as indicated by oxygen saturation will be lower with increasing postnatal age in response to hypoxic challenge.

For the analysis of the arousal response to the hypoxic and hypercarbic challenges, only the 8 subjects who were studied twice were

Table 3

Combined Arousal Response to Hypoxic and Hypercarbic Challenges (n=16)

Arouse to 2, 4, and 6% Carbon Dioxide



Diagonal A - Subjects responding similarly to hypoxia and to hypercarbia

Diagonal B - Subjects responding differently to hypoxia and to hypercarbia

*Numbers in parentheses represent early and later postnatal age, respectively.

eligible for analysis. During the hypoxic challenge at the later postnatal age, one subject had an arousal response in association with an apnea that precipitously decreased the oxygen saturation to 68%. Since the oxygen saturation at arousal at the second sleep study for the other subjects was in the 90s and arousal was not associated with apnea, this response represented a statistical outlier and was not representative of the group data. Thus this subject was excluded from

analysis, leaving 7 paired subjects for analysis in response to the hypoxic challenge and 8 paired subjects for analysis in response to the hypercarbic challenge.

In the analysis of the arousal response to the hypoxic and hypercarbic challenges, there is no overlap in either the postnatal age or postconceptual age for the early versus late ages (see Tables 4 and 5). Characteristics of the response to the hypoxic challenge and oxygen saturation at both postnatal ages is shown in Table 4. For the total group, oxygen saturation by postnatal age (early versus late) was statistically significant (matched pair signed test; $p = .016$). Arousal occurred in 4 out of 7 (57%) subjects at the early postnatal age in response to the hypoxic challenge compared to 2 out of 7 (27%) who aroused at the later postnatal age. There was not a significant difference in the mean oxygen saturation either for those who aroused or for those who did not arouse by postnatal age (85.5% versus 96% and 87% versus 94% respectively; Mann Whitney U; $p = .13$ and $p = .14$, respectively). Thus, there is no evidence from the data to support the hypothesis that arousal threshold will be lower with increasing postnatal age in response to the hypoxic challenge. However, for both those who aroused and those who did not arouse, the oxygen saturation was higher by postnatal age, but not statistically significant, probably due to the small numbers in each subgroup. Comparison of those who aroused with those who did not arouse within each postnatal age group was not statistically significant (85.5% versus 87% and 96% versus 94%).

In response to the hypoxic challenge, there was a mean increase in respiratory rate of 8 breaths per minute, compared to the baseline respiratory rate at the early postnatal age and a mean increase of 11

Table 4

Characteristics of Arousal Responses to Hypoxic Challenge at Two Postnatal Ages

		Early Postnatal Age (n=7)	Later Postnatal Age (n=7)
Postnatal (median, range) (weeks)		7 (6-11)	15 (12-16)
AGE: Postconceptual (median, range) (weeks)		37 (35-38)	45 (40-45)
Total Group SaO_2 (torr):	Mean:	86.1%	94.5% *
	Range:	73-93	90-98
Number arousing to 17% O_2		4/7 (57%)	2/7 (29%)
SaO_2 at arousal to 17% O_2 (torr):	Mean:	85.5%	96%
	Range:	73-93	94-98
SaO_2 at end 17% O_2 (torr)			
Non-Arousers:	Mean:	87%	94%
	Range:	81-93%	90-98%
Mean change from baseline SaO_2 (torr)			
Arousers:	Mean:	11.4	3
Non-Arousers:	Mean	12	4

O_2 = Oxygen

SaO_2 = Oxygen saturation

*Statistically significant

Table 5

Characteristics of Arousal Responses to Hypercarbic Challenge at Two Postnatal Ages

		Early Postnatal Age (n=8)	Later Postnatal Age (n=8)
AGE: Postnatal (median, range) (weeks)		7 (5-11)	15 (12-16)
Postconceptual (median, range) (weeks)		37 (35-38)	45 (40-45)
Total Group $TcPCO_2$ (torr):	Mean:	45.6%	45.5
	Range:	34-70	40-48
Number arousing to CO_2		7 (88%)	3 (38%)
2%		1	0
4%		2	1
6%		4	2
$TcPCO_2$ at arousal (torr):	Mean:	46	43.6
	Range:	34-70	38-48
$TcPCO_2$ at end of 6% (torr) Non-Arousers:	Mean:	43	46.6
	Range:	*	40-55
Mean change from baseline $TcPCO_2$ (torr) Arousers:	Mean:	5	4.6
Non-Arousers:	Mean:	*	5.8

CO_2 - Carbon dioxide

$TcPCO_2$ - Transcutaneous carbon dioxide

*Not able to calculate (n=1)

breaths per minute at the later postnatal age. Two subjects at the early postnatal age and two at the later postnatal age (not the same subjects) had periodic breathing at the end of the hypoxic challenge. The respiratory rates for these 4 subjects were not included in the above description.

Hypercarbic Challenge and Arousal Response

Hypothesis 4. Arousal threshold as indicated by transcutaneous carbon dioxide tension will be lower with increasing postnatal age in response to the hypercarbic challenge.

Characteristics of the response to the hypercarbic challenge at both postnatal ages is shown in Table 5. For the total group, transcutaneous carbon dioxide tension by postnatal age was not statistically significant (matched paired signed test; $p = .46$). Arousal occurred in 7 of 8 subjects (88%) at the early postnatal age in response to increased inspired carbon dioxide, compared to 3 out of 8 (38%) who aroused at the later postnatal age. There was not a significant difference in the mean transcutaneous carbon dioxide tension either for those who aroused or for those who did not arouse by postnatal age (46 versus 43.6 torr and 43 versus 46.6 torr, respectively). Thus, there is no evidence from the data to support the hypothesis that the arousal threshold will be lower with increasing postnatal age in response to the hypercarbic challenge. Comparison of those who aroused with those who did not arouse within each age group was also not statistically significant (46 versus 43 torr and 43.6 versus 46.6 torr, respectively). In response to the hypercarbic

challenges there was a mean increase in respiratory rate of 16 breaths per minute at the end of the challenge compared to the baseline respiratory rate. This increase was not different by postnatal age. By observation of the recordings, there was also an increase in the depth of respiration with each increase in inspired carbon dioxide (See Appendices F-I).

Summary of the Findings

Table 6

Summary of Findings

Relationships	Data Analysis	Findings
Condition under which apnea occurred (baseline or hypoxic challenge) and:		
1. lowest oxygen saturation	Mann Whitney U	N.S.
2. duration of apnea	Mann Whitney U	N.S.
3. beginning oxygen saturation	Mann Whitney U	p = .049
Condition under which apnea occurred (baseline or hypoxic challenge) and:		
1. arousal response	Chi Square	N.S.
2. type of apnea	Chi Square	N.S.
Arousal/non-arousal response by type of apnea	Chi Square	N.S.
Lowest oxygen saturation during apnea by type of apnea	Mann Whitney U	N.S.
Lowest oxygen saturation during apnea by duration of apnea	Spearman's rho	N.S.
Arousal/non-arousal response to apnea by duration of apnea	Mann Whitney U	p = .031
Arousal response to apnea by 3 predictor variables	Logistic regression	N.S.

Table 6 (cont.)

Summary of Findings

Relationships	Data Analysis	Findings
Rate of spontaneous arousals during baseline sleep by both postnatal age and sleep state	Repeated measures analysis of variance	p = .005 p = .001
Arousal response to hypoxic and hypercarbic challenges by postnatal age	Matched pairs sign test	N.S.
Oxygen saturation (for total group) in response to hypoxic challenge by postnatal age	Matched pair signed rank test	p = .016
Oxygen saturation at arousal to hypoxic challenge by postnatal age (arousal)	Mann Whitney U	N.S.
Oxygen saturation at end of hypoxic challenge (non-arousers) by postnatal age	Mann Whitney U	N.S.
Oxygen saturation for arousers/non-arousers by early postnatal age	Mann Whitney U	N.S.
Oxygen saturation for arousers/non-arousers by later postnatal age	Mann Whitney U	N.S.
Carbon dioxide tension (for total group) in response to hypercarbic challenge by postnatal age	Matched pair signed rank test	N.S.
Carbon dioxide for arousers/ non-arousers by later postnatal age	Mann Whitney U	N.S.

CHAPTER VI

DISCUSSION OF THE FINDINGS

The findings are discussed in relation to the hypotheses and in relation to findings from other studies. The latter part of the chapter addresses the conclusions and implications for future research.

Apnea and Arousal Response

Spontaneous arousal at the end of apnea has not been thought to be a common occurrence in premature newborns (Henderson-Smart & Cohen, 1988), even though the arousal response is considered to be an important protective mechanism against adversive respiratory events during sleep (Phillipson & Sullivan, 1978). No known previous study has addressed the question of behavioral arousal in response to apnea in prematures. In this study of prematurely born infants, at a median postnatal age of 7 weeks, studied just prior to hospital discharge, less than half (14/34) of the apneas between 6 and 24 seconds duration were terminated by a behavioral arousal response. In the remaining apneas, breathing resumed spontaneously without any evidence of behavioral arousal. Thus, in this study the hypothesis that apnea is terminated by an arousal response was not, in general, supported. It is acknowledged that while behavioral arousal may be clinically practical as an indicator of stimulation of the reticular activating system (RAS) and thus of respiration, it is not a precise indicator of more subtle changes that may be occurring, such as chemoreceptor stimulation of breathing by

hypoxia or by hypercarbia or by stimulation of RAS with changes from one sleep state to another. As has been noted by Krieger and Kurtz (1978), not all apneas in adults show evidence of electroencephalographic (EEG) changes with resumption of breathing following apnea. However, this tended to occur only in stages 3 and 4 NREM sleep, a stage of sleep not identifiable by EEG in infants until about 3 months of age.

In the present study arousal response was significantly related to apnea duration. This suggests that the longer the apnea, the more likely that physiological changes such as hypoxemia, hypercarbia and hemodynamic changes may be interacting to contribute to an arousal response.

The finding in this study that arousal response by type of apnea was not significantly related may be due to the small number of subjects in this study. No other studies have addressed arousal responses in relation to types of apnea in prematures or older infants. Since for adults with obstructive sleep apnea, arousal is considered to the be primary factor terminating the obstructive apnea, by activation of the upper airway dilatory muscles (Sullivan, Issa, Berthon-Jones, & Saunders 1984), the termination of obstructive apneas in the present study was examined in relation to arousal or changes in sleep state. Of the 8 obstructive apneas, 7 occurred during rapid eye movement (REM) sleep and of these, five were terminated by arousal. In the other 3 events, there was no change in sleep state from either REM or NREM. The occurrence of central apneas (n=26) was equally divided between REM or NREM sleep. Of the 17 central apneas that did not terminate in arousal, 15 remained in the same sleep state with only 2 changing from a deeper (NREM) to a lighter (REM) sleep. Since both apnea and an impaired arousal from

sleep have been postulated to play a role in sudden infant death syndrome (SIDS), it is important to begin to describe the relationship between apnea and arousal. The relationship between obstructive apnea and arousal response may be of particular concern because: 1) obstructive apnea has been postulated to play a role in both SIDS and in apparent life threatening events (ALTE), 2) because oxygen saturation has been noted to decrease more rapidly in obstructive apnea (Weil, Kryger, & Scoggin, 1978; Tilkian, Guilleminault, Schroeder, Lehrman, Simmons, & Dement, 1976), and 3) conventional apnea monitors used in both hospitals and in the homes do not detect obstructive apnea, but alarm only to the resultant decrease in heart rate.

The lowest oxygen saturation during apnea by either type or duration of apnea were not statistically significantly related in the present study. Muttitt, Finer, Tierney, and Rossman (1988) also recently reported no significant difference in mean decrease in oxygen saturation by type of apnea in prematures. However, these same investigators reported a significant correlation between apnea duration and decrease in oxygen saturation. This difference in findings may be due in part to: 1) a larger sample size in their study (n=27, with 1266 apneas), 2) the fact that 14.4% had oxygen saturation of less than 85% preceding an apnea, and 3) the age of the subjects (between 1 and 21 days of age) at the time of study was much younger and perhaps were still influenced by the biphasic response to hypoxia. In the Muttitt, Finer, Tierney, and Rossman (1988) study, the subgroup with the lower oxygen saturation prior to apnea experienced a significantly greater decrease in oxygen saturation during apnea than those with oxygen saturations of greater than 85% prior to apnea. In the present study,

the oxygen saturation preceding apneas during baseline sleep ranged from 92 to 99%, with a mean 96%. In adults, the rate of fall in oxygen saturation during sleep apnea is primarily dependent on the oxygen saturation at the onset of apnea (Strohl & Altose, 1984). In prematures with a much smaller reservoir of oxygen in the lungs, it would be expected that the oxygen saturation prior to apnea in prematures would be an even greater determinant of both the rate of fall of oxygen saturation and the lowest oxygen saturation reached during an apnea.

Apnea is the most common problem of control of breathing in the preterm and is often interrupted by nurses providing tactile stimulation. At the same time it is also a frequent observation that in the very low birth weight (and low gestational age) neonate, tactile stimulation precipitates apnea. In prematures, stimuli such as degree of arousal and tactile stimuli influence breathing to a greater degree than at later ages. Little is known about the development of the arousal response, especially in the immediate postnatal period, if or how this response relates to apnea termination or if arousal mechanisms are different for central and obstructive apneas in infants. Kelly, Stellwagen, Kaitz, and Shannon (1985) postulate that the mechanisms needed to terminate apnea are as mature at one month as they are at one year of age. However, this is based on observations of full-term healthy infants throughout the first year of life, in which apneas of 10 to 12 seconds occurred only occasionally, but did not decrease significantly with increasing age. Whether a similar pattern occurs in prematures is not known.

Each of the 3 predictor variables have been identified as contributing to the arousal response. Hypoxia (indicated in this study

by the lowest oxygen saturation reached during the apnea) stimulates arousal from sleep (Bowes, Townsend, Kozar, Bromley, & Phillipson, 1981b). Bradycardia occurring in conjunction with apnea in prematures has been shown to be associated with transient increases in blood pressure and pulse pressure (Girling, 1972), and both acute increases (Fewell & Johnson, 1984) and decreases (Walker, Horne, Bowes, & Berger, 1986) in blood pressure are associated with arousal from sleep in the newborn animal model. From experiments with newborn lambs, Fewell and Baker (1988) suggest that arousal was dependent on the rate of change of arterial oxygen. The finding that none of the 3 predictor variables were statistically significant in predicting an arousal response may again be due to the small number of subjects in this study. In addition, it must be noted that logistic regression assumes that all observations are independent (i.e., all different subjects). In fact, the 34 observations came from 9 different subjects and, thus, the data are not truly independent. However, any statistical correction for this non-independence would only result in less statistical significance and hence the findings of non-significance would not change.

Postnatal Age and Arousal Response

In the present study, the rate of spontaneous behavioral arousals during baseline sleep was significantly lower at the later postnatal age compared to the earlier postnatal age. This finding does not support the hypothesis that behavioral arousal responses would increase with increasing postnatal age, based on the postulation that the arousal threshold is high in fetal life (Walker, 1986) and early postnatal

life (Bowes, 1982). The finding, however, is in agreement with data on the changes in sleep organization that occur during the first year of life; specifically that at approximately 11 to 12 weeks of life the amount of NREM sleep and waking time increases, while the amount of REM sleep decreases. There is also a redistribution of sleep-wake cycles, such that the longest sleep period increases to eight hours, and the majority of sleep occurs during the night in NREM sleep (Navelet, Benoit, & Bouard, 1982; Sterman & Hodgman, 1988; Gould, Lee, & Morelock, 1988). Concurrent with these changes in sleep patterns at about 3 months of age, there are also decreases in heart rate, heart rate variability, respiratory rate and respiratory variability (Sterman & Hodgman, 1988). These changes are occurring at the time that coincides with the peak incidence of SIDS. Gould (1983) believes that the maturation of the central nervous system which results in prolonged sleep at this particular critical period of development and the ability of the infant to meet homeostatic demands that occur during sleep, (like arousal in response to respiratory or cardiac disturbances) is critical in the development of SIDS.

The finding of decreased arousals with increasing postnatal age also needs to be considered from another perspective. For example, the postnatal age of the subjects at the time of the first sleep study was 7 weeks (median, range 4-12). There are currently no studies that address the developmental pattern of arousal responses from birth in human premature newborns and, without knowing the preceding pattern of arousal, it is not possible to put these findings at 7 weeks postnatal age into their proper context or perspective or permit full interpretation of their meaning. Milerad, Hertzberg and Lagercrantz's

(1987) longitudinal study of healthy full- term newborns found that in response to breathing 15% oxygen, arousal occurred in 3 out of 10 infants studied between 1 and 5 days, in 6 out of 12 studied between 4 and 8 weeks, and in 2 out of 13 studied between 10 and 14 weeks of postnatal life. Although the numbers in this study are obviously small, it does suggest a changing arousal response to the same stimulus with increasing postnatal age. In the present study there was also a decrease in arousal response to the hypoxic and hypercarbic challenges at the later postnatal age compared to the response at the earlier age, although it was not statistically significant. Thoppil, Belan, Cowen, and Mathew (1989) found preterm infants to have a higher arousal rate per minute than term infants. It is not known how changes in arousability emerge during early postnatal life and if arousal is related to other developmental changes that are occurring during this time.

In addition, the subjects in the present study had spent all of their postnatal life up to the time of the first sleep study in an intensive and intermediate nursery with its attendant 24 hour light and auditory stimulation, multiple caregivers and irregular, often intrusive, caretaking activities. The effect of this environment on the premature infants' ability to regulate and to maintain a stable sleep state has not been adequately addressed. Also, the time of observations in this study was limited to approximately a 3-4 hour period. It is not known how representative this time is of the total 24 hour period, for the variables under study.

The finding in the present study of a significantly increased rate of arousals during REM sleep compared to NREM sleep at both postnatal

ages is in agreement with the speculation that brief arousals during REM sleep may be a reflection of phasic central nervous system stimulation (Roffwarg, 1966; Coons, 1987). REM sleep decreases while waking time increases with increasing age and meets the need for central nervous system stimulation. Infants less than 6 months of age, who have experienced ALTE have been noted to have fewer arousals and less body movements during sleep (Coons & Guilleminault, 1985). A deficient arousal responsiveness has been postulated as a possible cause of Sudden Infant Death Syndrome (SIDS). An impaired or deficient arousal response in potential SIDS infants could prevent them from responding to episodes of sleep related apnea. Previous studies of infants with apparent life threatening events (ALTE) have identified delayed initiation of mouth breathing after nasal occlusion during sleep and decreased colic associated night awakenings (Swift & Emery, 1973; Weissbluth, 1981). Thus, behavioral arousal to a wide variety of stimuli may be decreased in infants at risk for SIDS. Arousal responses to just one stimuli, hypoxia, and during just one state, sleep, have been studied most, but arousal responsiveness may need to be considered in a variety of situations during awake and sleep states (Hunt, 1988).

Hypoxic and Hypercarbic Challenge and Arousal Response

In response to the hypoxic challenge there was a significant difference in the mean oxygen saturation by postnatal age, when the total groups were compared; however there was no statistical difference by arousal status (arousers or non-arousers) and postnatal age. The mean oxygen saturation was higher at the later postnatal age, both for

those who aroused and for those who did not; however, the small number of subjects in the sub-groups contributes to the finding of non-significance.

The normal response to hypoxemia during sleep is to arouse and thus reverse the hypoxic stress. The ability to arouse may be an important component of the respiratory control system. The level of hypoxia at which arousal occurs, however, is very variable. For example, in testing normal healthy adults, Berthon-Jones and Sullivan (1982) found a failure to arouse by 70% oxygen saturation in nearly one half of the hypoxic tests. In normal healthy infants serving as control subjects, McCullock, Brouillette, Guzzetta, and Hunt (1982) found that 30% failed to arouse to hypoxia. It is possible that an arousal threshold could reliably be produced at a certain low oxygen saturation, but this level is too low to be achieved safely in human studies. For example, cats have been reported to have an arousal threshold at 30-50% oxygen saturation (Neubauer, Santiago, & Edelman, 1981).

The hypoxic challenge is used both for clinical decision making and for research to evaluate the infant's ventilatory and arousal responses, and, thus, how the infant might respond to apnea. Of the five subjects who aroused at early postnatal age, four also had apneic episodes during the sleep study. However, these same subjects did not always arouse to apnea, even if the oxygen saturation was lower with the apnea than it was with the hypoxic challenge. The stimulation of the chemoreceptors precipitated by apnea and by the hypoxic challenge differ in ways that may be important in the response. For example, with apnea, the rate of fall of oxygen saturation is generally very rapid; in the present study the rate of fall of oxygen saturation in response to apnea ranged from

less than 1 torr/second to greater than 2.5 torr per second. With central apnea there is no airflow in the nares and upper airway. With the hypoxic challenge, the decrease in oxygen saturation occurs over a longer time period, and arousal, when it did occur, in the present studies, occurred between 6 and 13 minutes after the onset of the hypoxic challenge. Respiratory rate and depth generally increase with the hypoxic challenge, thus increasing airflow in the nares and upper airway. With obstructive apnea, respiratory efforts against a closed glottis produce proprioceptive stimulation, which may contribute to arousal, but which is not seen with the hypoxic challenge. Thus, the hypoxic challenges may not be an adequate simulation of what happens during apnea and this may contribute to the challenge not being considered sensitive or predictive of sudden infant death (SIDS) or of apparent life threatening events (ALTE).

In response to the hypercarbic challenge there was no significant difference in the mean transcutaneous carbon dioxide tension for the total group by postnatal age, or for the two postnatal age groups by arousal status. Hypercapnia is a potent stimulus to ventilation and all subjects increased their rate and depth of ventilation sufficient not to increase their arterial carbon dioxide.

In relation to the proposed model (Figure 2, Chapter 1) the findings supported a significant relationship between the rate of occurrence of spontaneous behavioral arousal during baseline sleep and postnatal age and sleep state. Thus, it seems logical that before considering behavioral arousal as an outcome variable in response to respiratory events, (i.e., apnea, hypoxic or hypercarbic challenges), these events must first be considered within the context of postnatal

age and sleep state. The rate of behavioral arousal in response to the hypoxic and hypercarbic challenges was decreased with increasing postnatal age, but not significantly; however, this may reflect the small number of subjects. The model did not support in general a relationship between behavioral arousal and apnea termination; however, this finding needs to be interpreted within the context of the age of the subjects at the time they were studied; studies of behavioral arousal in response to apnea in prematures of younger postconceptual ages may show a different response. Behavioral arousal in response to apnea was not significantly related to lowest oxygen saturation, suggesting at least at the age studied, that hypoxia may not be the potent stimulus to arousal as has been postulated. Behavioral arousal was significantly related to apnea duration, suggesting that the longer the apnea continues, that additional physiological factors interacting, such as hypercarbia, or hemodynamic changes, may contribute to an arousal response. Additional analysis of data from the present study should include the role, if any, of changes in transcutaneous carbon dioxide tension in contributing to behavioral arousal from apnea.

Conclusions and Implications for Future Research

It is concluded from the data of this study that: 1) the hypothesis that apnea in prematures is, in general, terminated by behavioral arousal response is not supported; 2) the hypothesis that the frequency of behavioral arousals, both spontaneous and in response to hypoxic and hypercarbic challenges, would increase with increasing postnatal age was not supported. Spontaneous behavioral arousals decreased significantly

during baseline sleep with increasing postnatal age and decreased, but not significantly, in response to the hypoxic and hypercarbic challenges with increasing postnatal age. The frequency of spontaneous arousals was significantly higher in REM compared to NREM sleep at both postnatal ages; 3) the hypothesis that arousal threshold as indicated by oxygen saturation values would be lower (i.e., mean oxygen saturation would be significantly higher) with increasing postnatal age in response to the hypoxic challenge was not supported; and 4) the hypothesis that the arousal threshold as indicated by the carbon dioxide tension would be lower with increasing postnatal age in response to the hypercarbic challenge was not supported. These findings suggest that at the postnatal age at which the subjects were studied, they were able to increase their ventilation sufficiently to maintain stable oxygen saturation and carbon dioxide tension in response to both challenges, without behavioral arousal.

Suggestions for future research include: 1) studies of the normal developmental course of arousal in both preterm and full-term infants to determine if there is a pattern in which arousal responses reach a nadir and whether that may coincide with other developmental patterns, such as the transition from infant to more adult type sleep at around 3 months of age and to determine if this increases the infant's vulnerability; 2) studies to further describe the relationship between apneas and other respiratory events and arousal responses in both prematures and full term newborns; and 3) studies of factors which may influence or impair the infant's ability to arouse, such as sleep fragmentation that may occur because of environmental influences (i.e., nursery environments) or because of illnesses; whether arousal response is impaired with

repeated exposure to hypoxemia is an important question for children with chronic obstructive sleep apnea. That an infant has apnea may not be as important as if that infant is able to defend and maintain physiological integrity.

A major limitation of the present study was the number of subjects. Studies need to have a larger sample size, allowing for inevitable sample attrition and for the fact that responses will fall into different categories, thus making the numbers for specific comparisons even smaller. Studies should be carried out longitudinally, thus increasing the cost and complexity of data collection and data analysis. However, since current critical questions in clinical practice are what constitutes a normal respiratory pattern in prematures at the time of hospital discharge and what is the relationship between respiratory patterns and subsequent life threatening events or SIDS, these studies may provide answers and directions for these clinical problems.

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APPENDIX A

UCSF Consent Form

Appendix A

University of California, San Francisco
Consent to Act as a Research Subject

Study of Arousal Response and Arousal Threshold
in Premature Newborns

1. I am being asked to have my baby participate in a research study conducted by Dr. William Tooley and Helen L. Dulock, RN, MN. The purpose of this study is to learn more about factors that influence breathing patterns during sleep in premature newborns.

2. As a subject in this study, my baby will be brought from the nursery to Pediatric Pulmonary Laboratory, 13th floor Moffitt Hospital, where he/she will be studied for 3-4 hours while asleep. As the parent(s) I/we may be present for any or all of the study and may participate in any care giving activities as would normally occur in the nursery.

3. During the study the following measurements will be made:
a. Discs will be attached to the baby's skin to monitor heart rate and transcutaneous oxygen and carbon dioxide.
b. Elastic (stretchy) bands will be placed around the baby's chest and around the abdomen to monitor respiration.
c. A clip will be placed on an extremity to measure oxygen saturation.

My baby will breathe different gas mixtures containing oxygen and carbon dioxide. The oxygen mixture will be approximately equivalent to that at 5,000 feet altitude and will be breathed for no more than 15 minutes during each study period. The carbon dioxide gas mixture will be breathed for no longer than 18 minutes during each study session.

These measurements are routinely done during sleep studies on prematures and older infants.

My baby will be studied for approximately 4 hours just prior to discharge from the nursery and at 3 months post conceptual age. The study will be conducted by Helen L. Dulock, under the direction and supervision of Dr. William Tooley. During the study any care needed by the baby will be provided, including usual care activities as feeding, comforting, or administering medications.

If any episodes of apnea (stop breathing) occur which cause the oxygen saturation to fall below 75%, appropriate interventions will be carried out (stimulation to breathe) and the physician in charge of the baby will be informed.

4. Risks/Discomforts:

Givingthe lower oxygen gas mixture may change the breathing pattern, (rate and depth) and may cause a decrease in the oxygen saturation which will not be allowed to decrease below 75%. Giving the carbon dioxide gas mixture may change the breathing pattern (rate and depth) and may cause the baby to arouse.

Approval # H1214-01768-03

The disc for measuring transcutaneous oxygen and carbon dioxide must be heated to 43 degrees Centigrade. There is a control on the device to prevent the disc from being heated above this temperature. The skin under the electrode may develop an area of redness, which usually disappears in less than 24-36 hours. There are no other known risks.

5. Benefits:

There will be no direct benefit to my baby for participating in this study, although the study will show whether or not he/she has episodes of periodic breathing and or apnea (stop breathing) and his/her response to them. It is hoped that in the future these kind of studies will lead to the identification of characteristics associated with stopping breathing during sleep in prematures and which babies need to have further monitoring of respiration and heart rate at home.

6. Alternatives:

The alternative to participating in this study is to receive the standard of care. The standard of care for babies less than 1500 grams (3 pounds, 5 ounces) at birth is to have only one sleep study as described above performed in Pediatric Pulmonary Laboratory prior to discharge from the hospital, with no follow up study. For babies weighing more than 1500 grams at birth the standard of care does not include having a sleep study as described above performed before discharge.

7. Injury:

If my baby is injured as a result of being in this study, treatment will be available. The cost of such treatment may be covered by the University, depending upon a number of factors. The University does not normally provide any other form of compensation for injury. For further information, I may call the Office of the Committee on Human Research at (415) 476-1814.

8. Questions:

Ms. Dulock has talked with me about this study. She is willing to answer my questions at any time. She can be reached at 476-1858 or 824-5089.

9. Participation:

Participation in this study is voluntary and I may decline to have my baby participate in this study or withdraw my baby from the study at any time without any jeopardy to his/her medical care.

10. Consent:

If I wish to have my baby participate in this study, I should sign this form.

I have been given a copy of this consent form and of the Experimental Subject's Bill of Rights to keep.

_____
Signature of mother

_____
Signature of father

_____ _____
Signature of witness Date

Approval # H1214-01768-03

APPENDIX B*

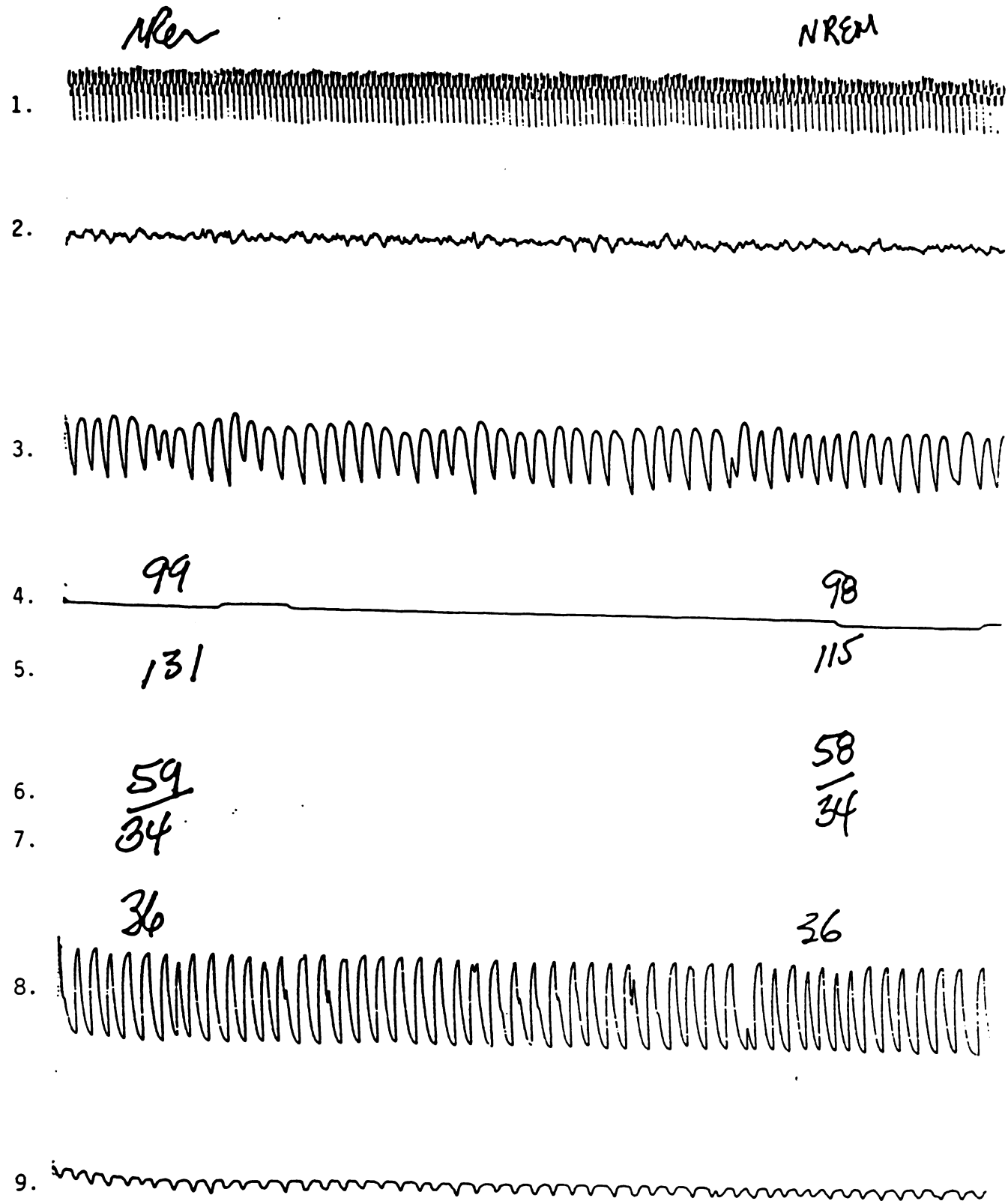
Example: Baseline Tracing

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Appendix B

Example: Baseline Tracing



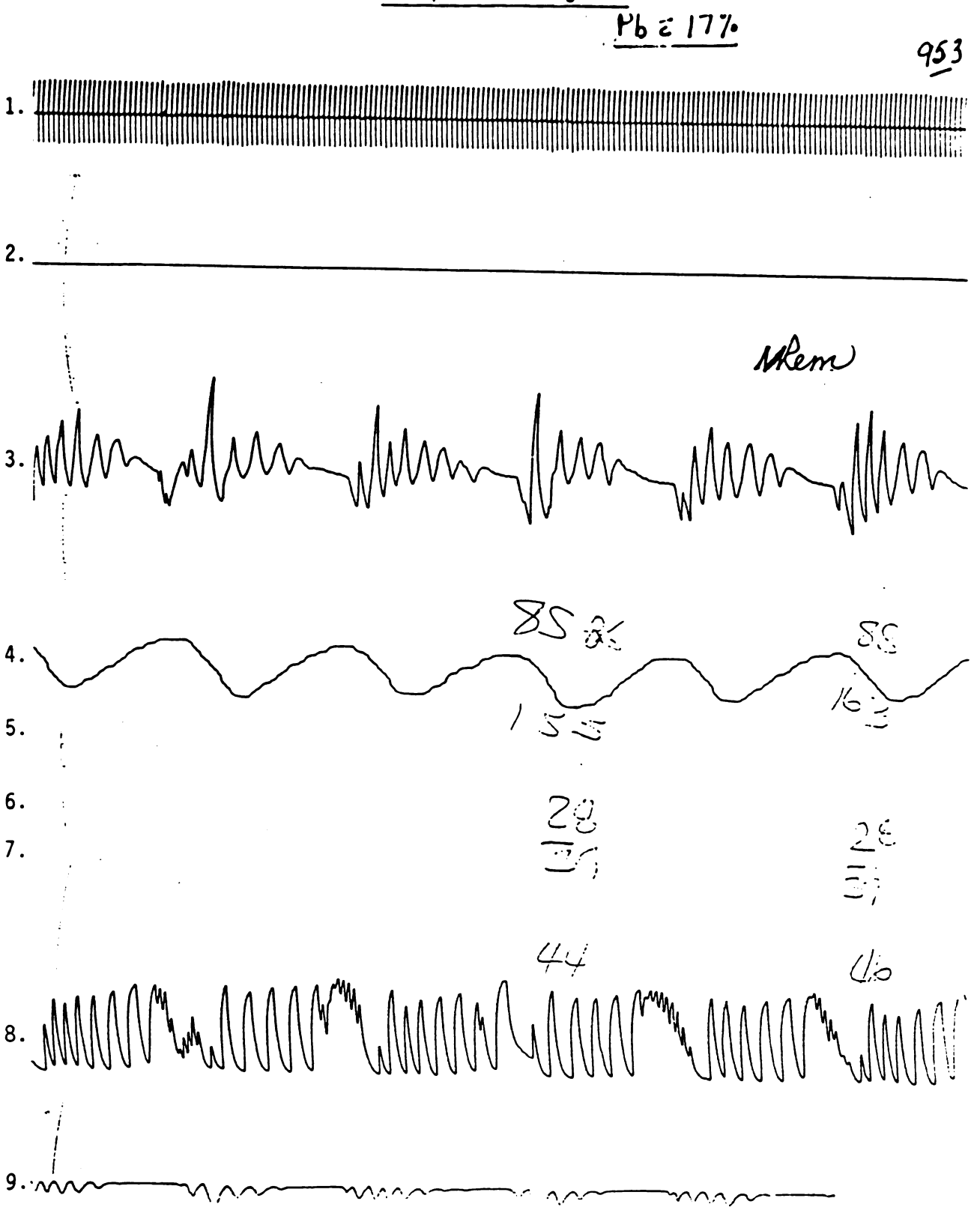
APPENDIX C*

Example: During 17%

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Example: During 17%



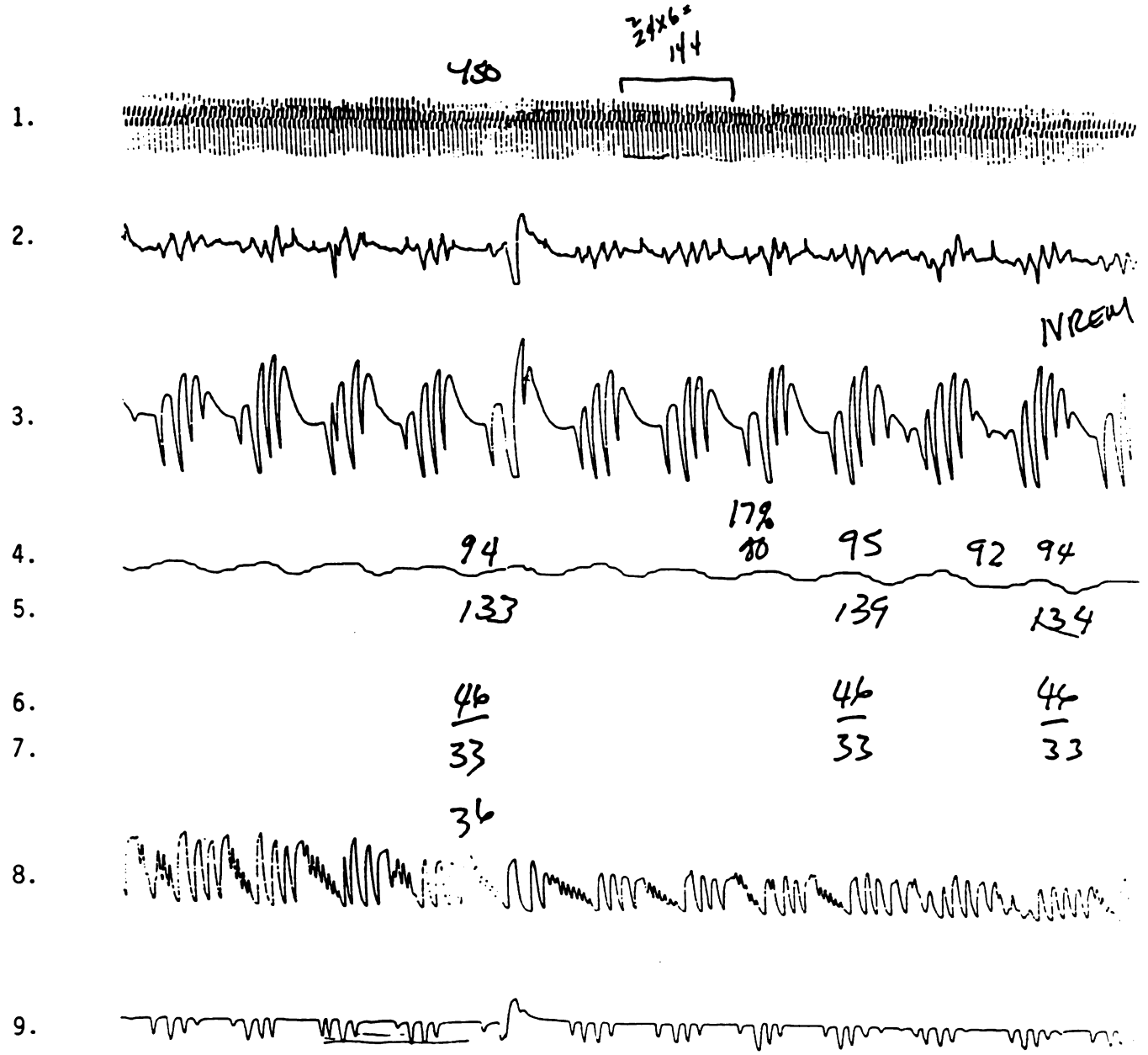
APPENDIX D*

Example: End of 17% Without Arousal

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Example: End of 17% without Arousal



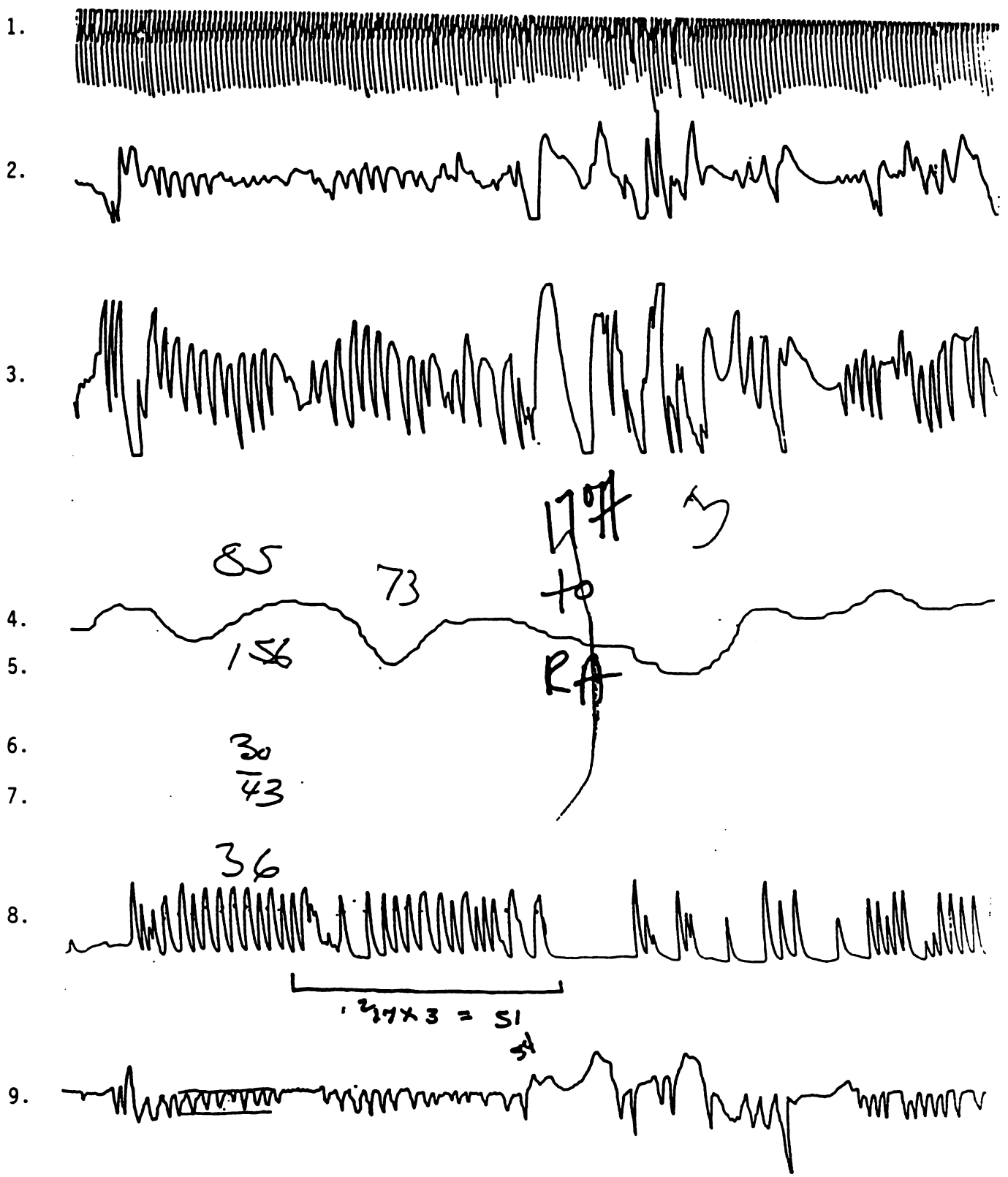
APPENDIX E*

Example: 17% Oxygen with Arousal

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Example: 17% Oxygen with Arousal



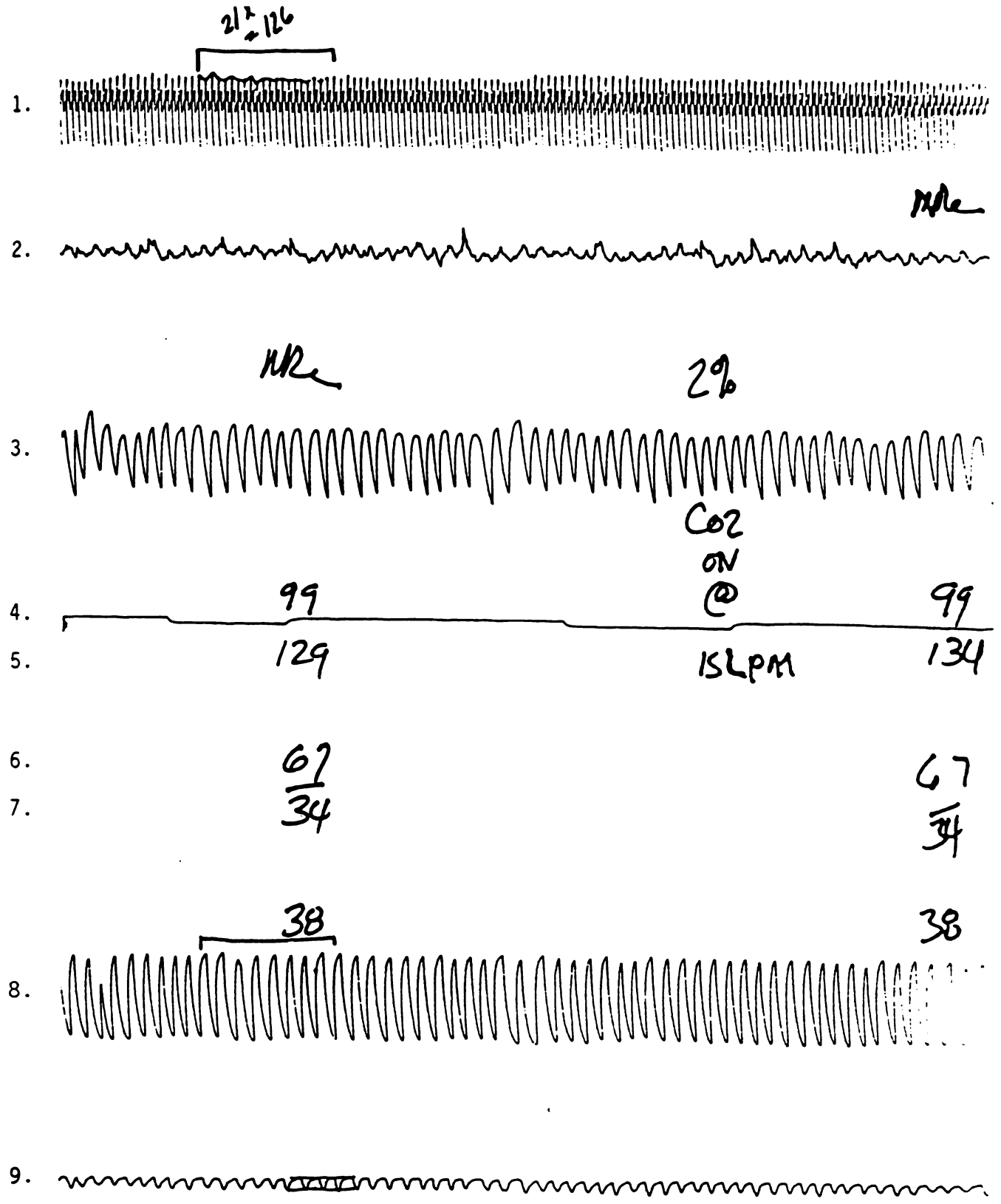
APPENDIX F*

Example: Initiating 2% Carbon Dioxide

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Example: Initiating 2% Carbon Dioxide



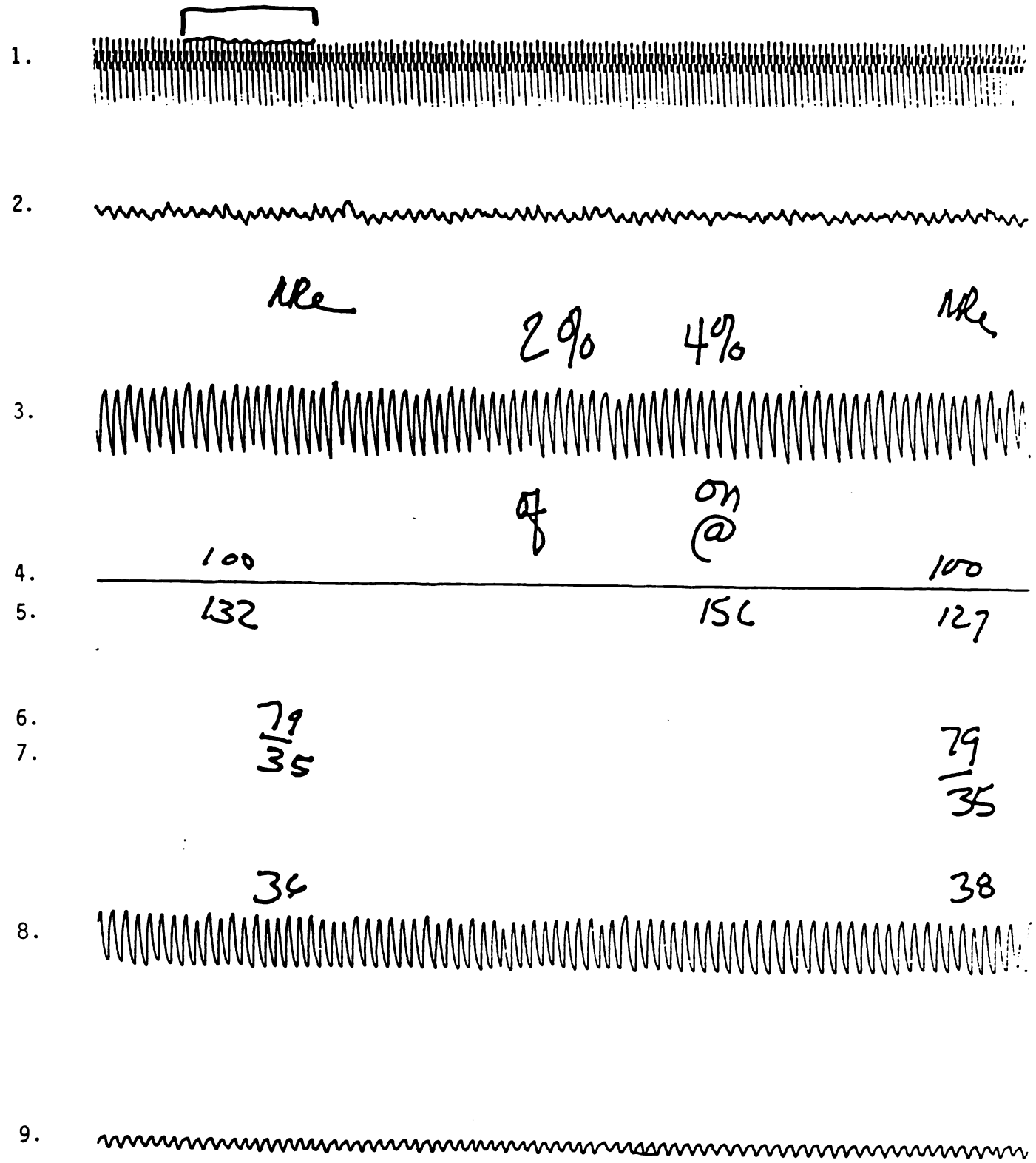
APPENDIX G*

Example: Changing from 2-4% Carbon Dioxide

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Example: Changing from 2-4% Carbon Dioxide



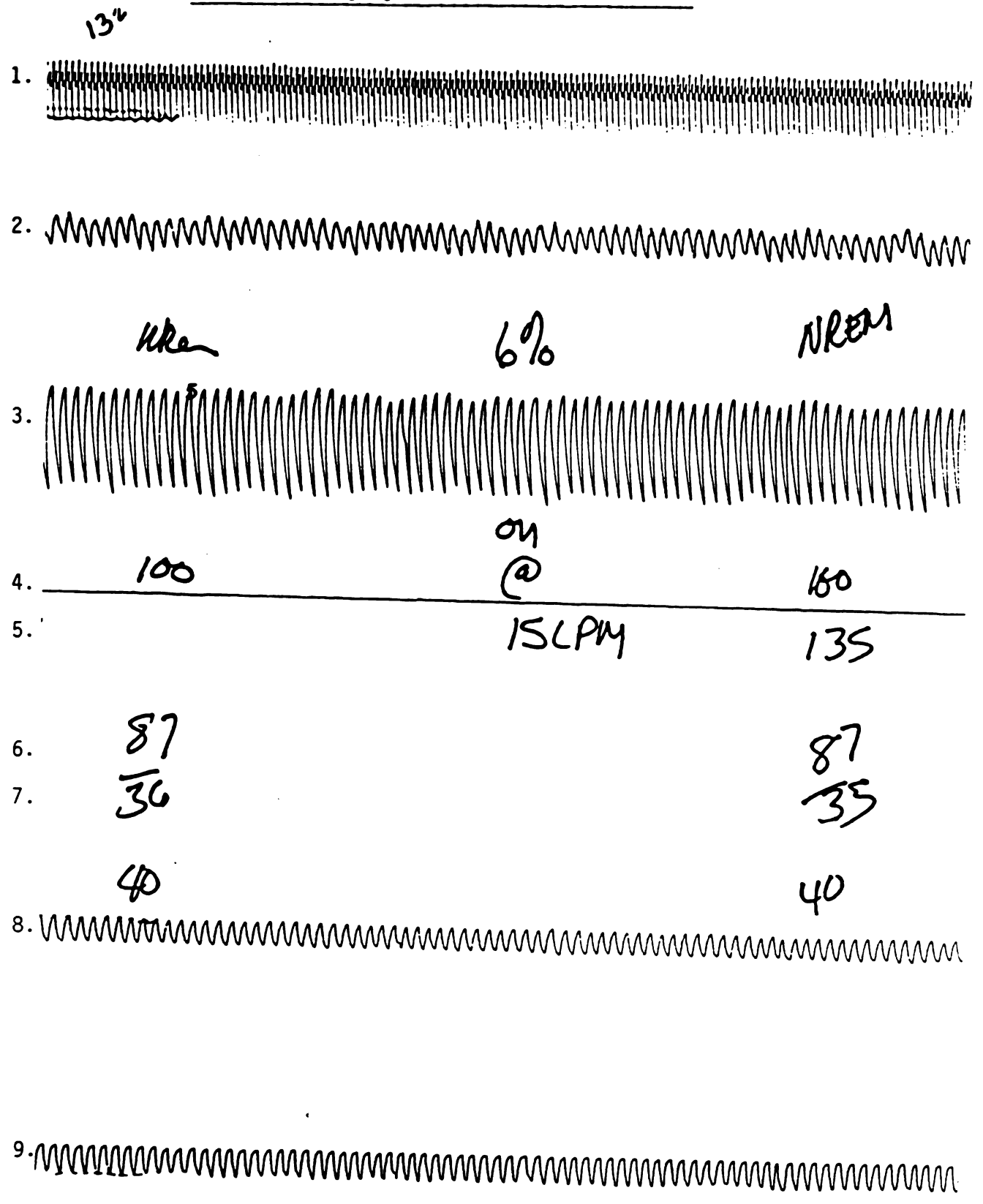
APPENDIX H*

Example: Changing from 4-6% Carbon Dioxide

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Example: Changing from 4-6% Carbon Dioxide



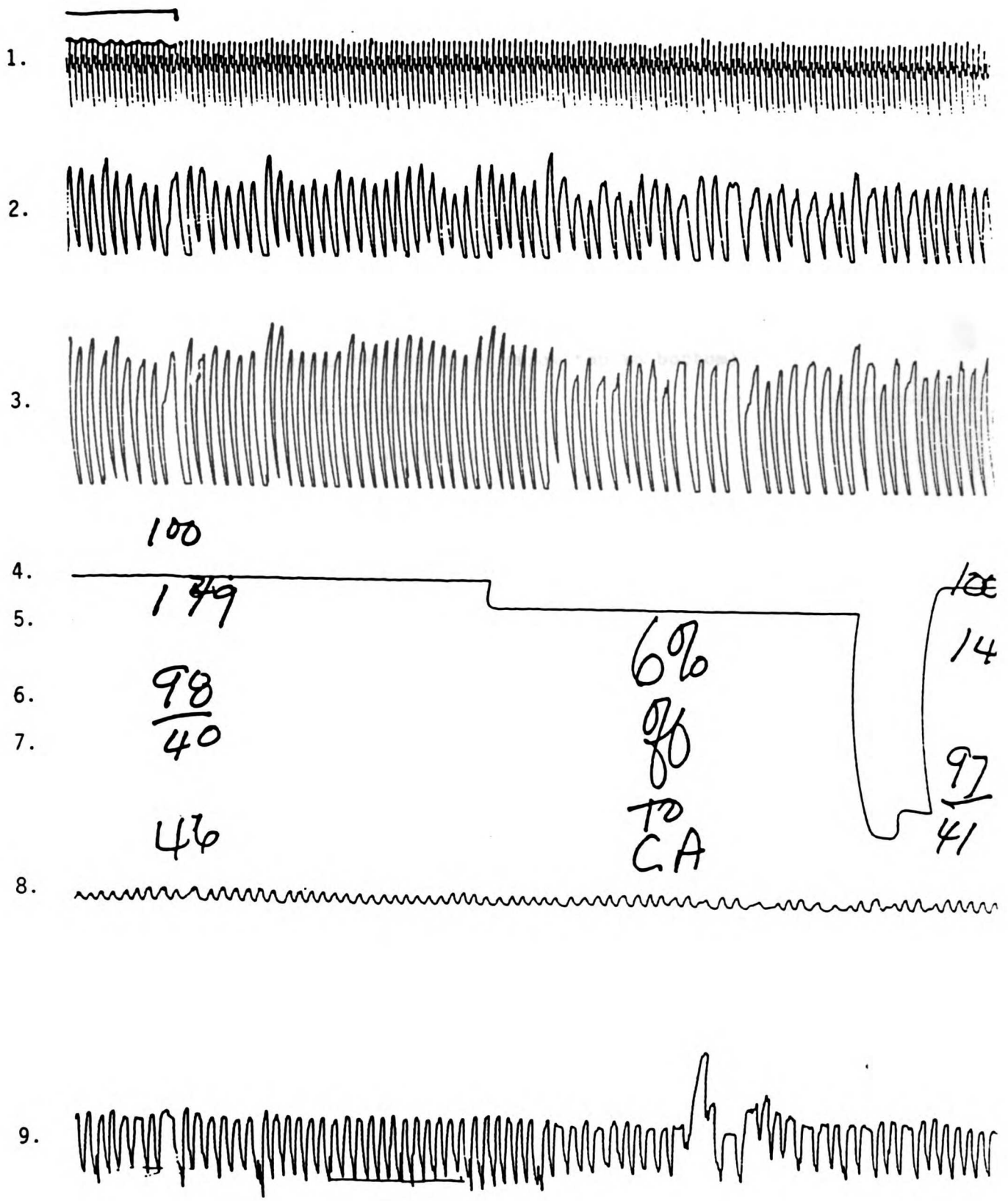
APPENDIX I*

Example: End 6% Carbon Dioxide Without Arousal

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Example: End 6% Carbon Dioxide without Arousal



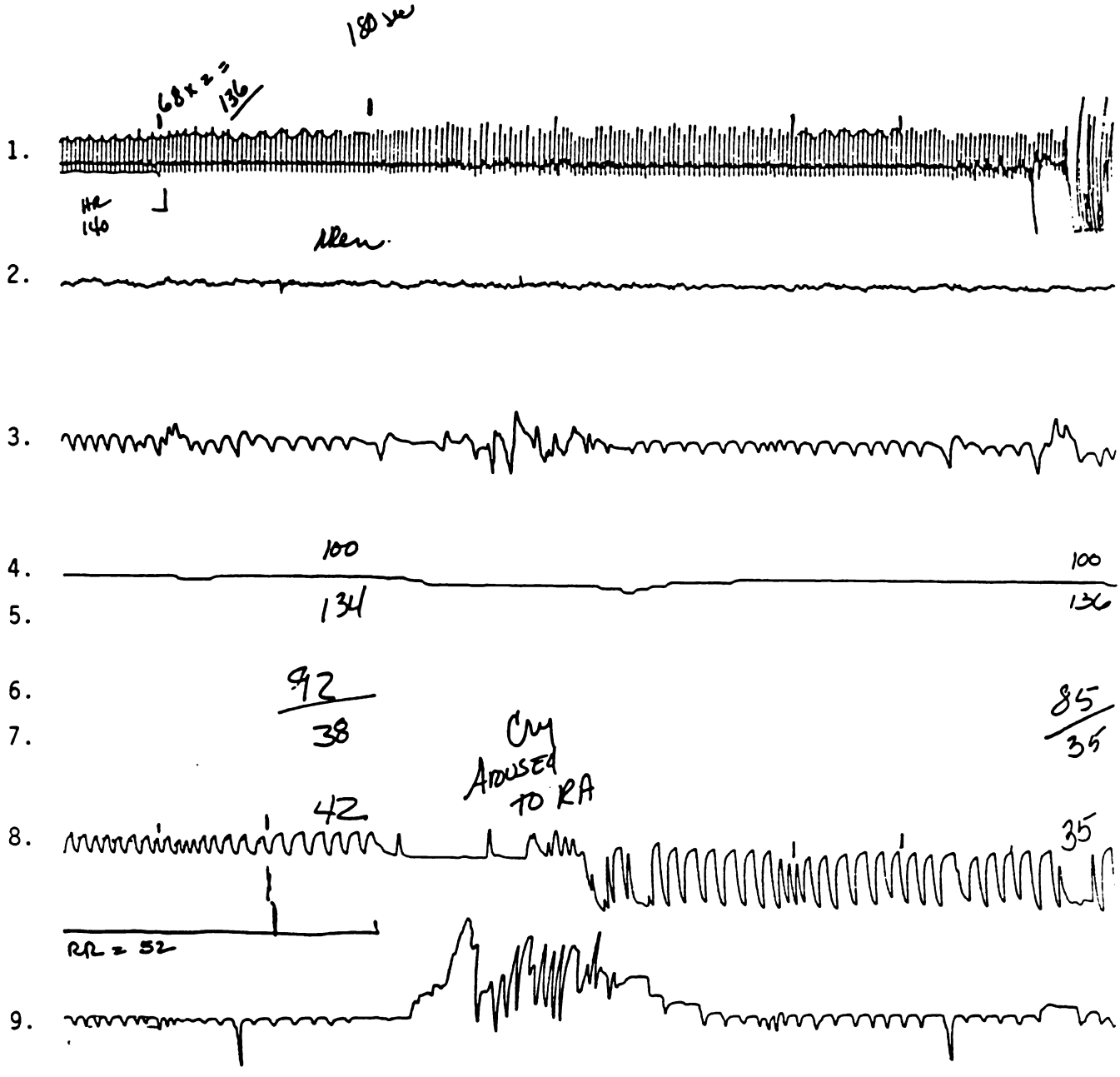
APPENDIX J*

Example: 6% Carbon Dioxide with Arousal

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Example: 6% Carbon Dioxide with Arousal



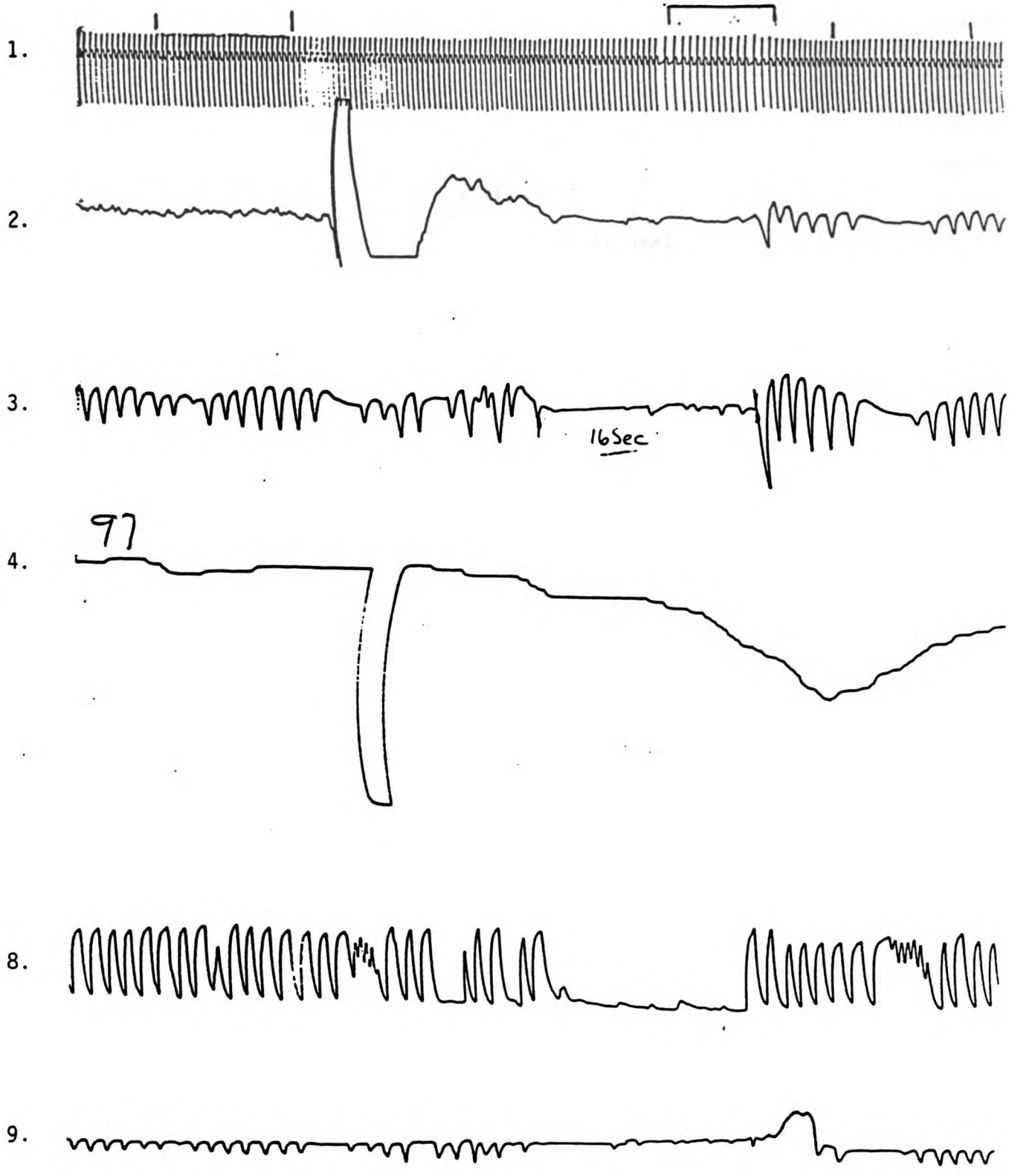
APPENDIX K*

Example: Apnea Without Arousal

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Example: Apnea without Arousal



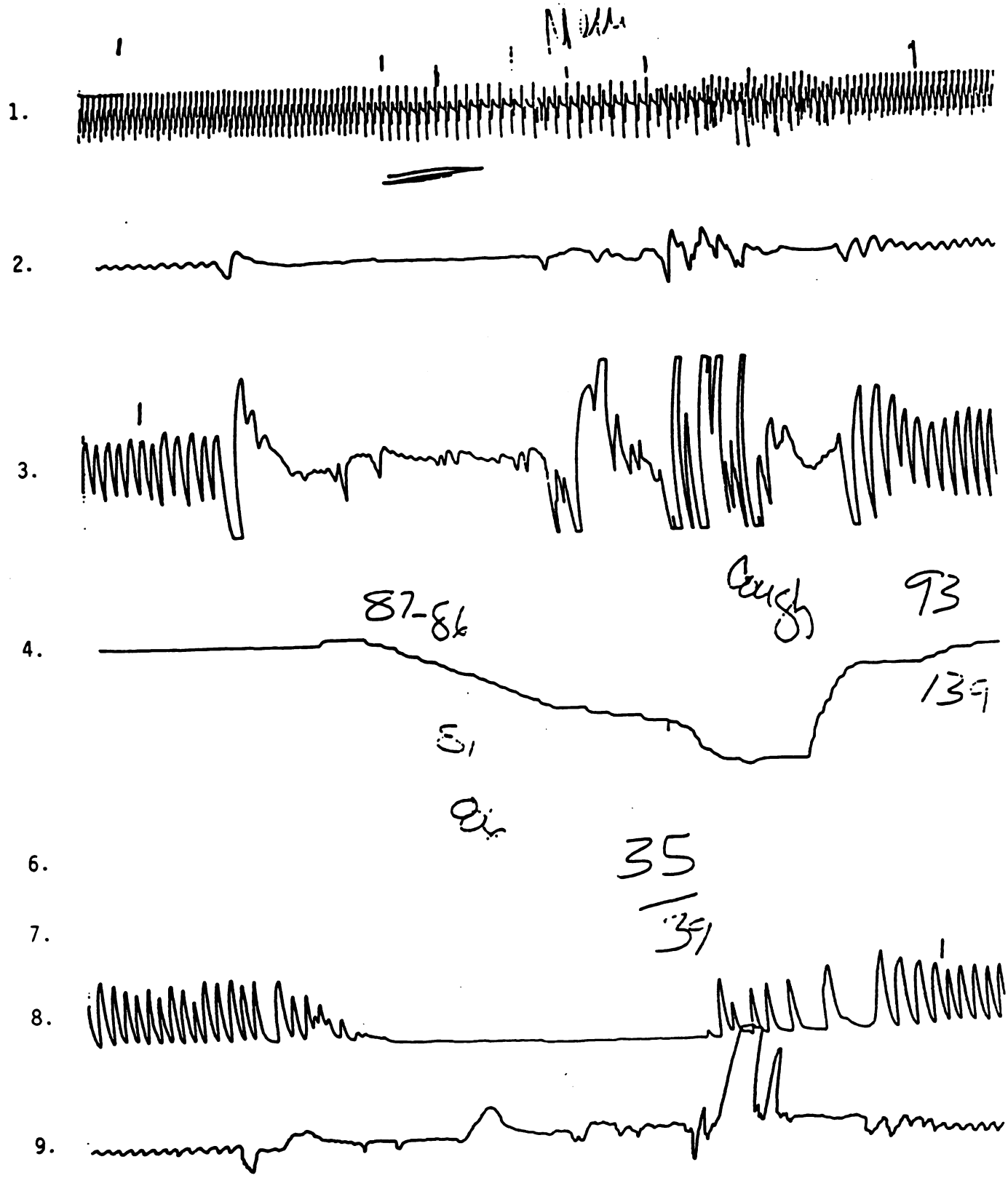
APPENDIX L*

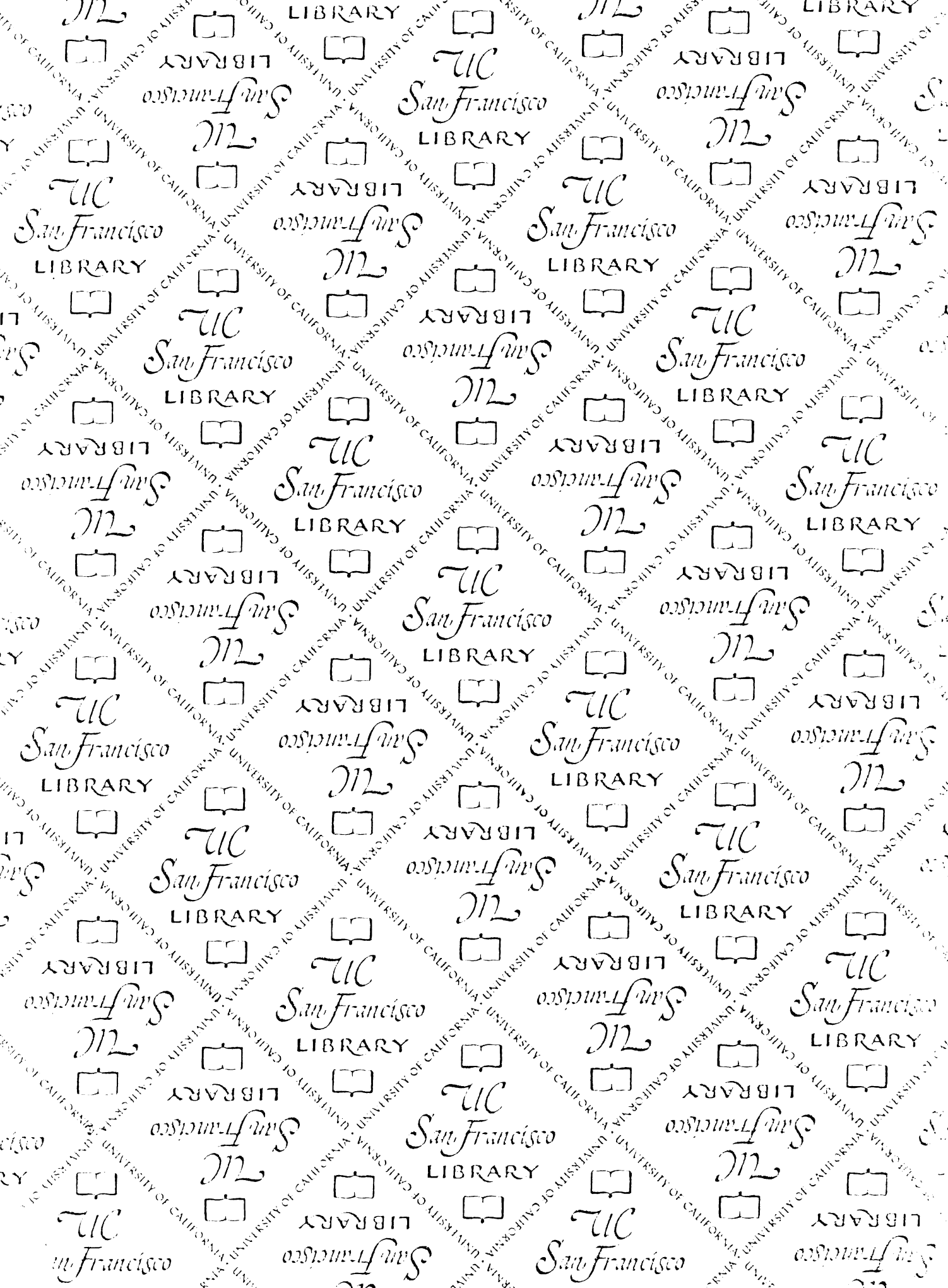
Example: Apnea With Arousal

*Legend for Tracings (from top to bottom)

1. Heart rate
2. Chest movement
3. Abdomen movement
4. Oxygen saturation
5. Pulse from oximeter
6. Transcutaneous skin surface oxygen
7. Transcutaneous skin surface carbon dioxide
8. Respired carbon dioxide
9. Esophageal pressure

Example: Apnea with Arousal

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