Evidence of a Critical Period of Airway Instability during Central Apneas in Preterm Infants

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The timing and magnitude of airway narrowing in central apneas is unknown. We have developed a method of apnea classification that relies on the transmission of cardiac airflow oscillation to indicate airway patency. Using a theoretical model, we showed that the amplitude of the cardiac airflow oscillation is proportional to airway diameter for small lumens. While in the majority of central apneas the amplitude of the cardiac airflow oscillation remains nearly constant, in a subset of events the waveform decreases with time, suggesting airway narrowing. We hypothesized that this is not a random occurrence but reflects a critical period of airway instability during central apnea. To test this hypothesis we studied 41 preterm infants. Of 4,456 central apneas, 585 had a decrease in the amplitude of the cardiac oscillation. The amplitude of the cardiac airflow oscillation during an apnea was recorded to provide a dynamic measure of changes in airway diameter with time. To allow for comparisons between patients the amplitude of each cardiac airflow oscillation was expressed as a proportion of the maximum amplitude observed in each infant. We then compared the amplitude at multiple successive 0.5 s intervals with the amplitude of the cardiac airflow oscillation observed at the apnea outset using ANOVA. We found a significant decrease in cardiac airflow oscillation after only 1 s irrespective of the apnea duration (3 to 16 s). We conclude that airway narrowing during central apnea is not a random occurrence but appears shortly after the onset of the apnea. We speculate that the phenomenon is secondary to passive airway relaxation. Lemke RP, Idiong N, Al-Saedi S, Kwiatkowski K, Cates DB, Rigatto H. Evidence of a critical period of airway instability during central apneas in preterm infants.

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Apnea is a common clinical problem in preterm infants (1, 2). Traditionally, it has been classified as central, obstructive, or mixed. Central apneas are those without associated respiratory efforts; obstructive apneas are those with respiratory efforts, and mixed apneas are those with efforts for part of the apnea. By definition, therefore, airway obstruction occurs only in obstructive and mixed apneas but not in central apneas. Some investigators, however, by directly visualizing the upper airway or measuring the point in the tidal cycle where apnea starts, have suggested that the airway frequently closes during central apnea (3, 4). They found that this closure occurs at the beginning of the apnea, raising the possibility that occlusion of the airway per se may be the cause for the apnea. Because respiratory efforts are absent, these apneas are central with a "silent obstruction."

Extrapolating from the work of Milner and coworkers (3, 4) we have recently devised a new method of classifying apneas based on the presence or absence of an amplified cardiac oscillation waveform observed in the respiratory flow tracing (5). Using this new method, central apneas are those with the oscillation present, obstructive apneas are those with the oscillation absent, and mixed apneas are those with the oscillation absent during part of the apnea. The new method is more accurate than the traditional method because it relies on an airway signal that disappears if obstruction is present and not on respiratory efforts occurring elsewhere in the body. More importantly, because the amplitude of the oscillation signal is related to airway diameter, it is possible to time changes in airway diameter with precision. We have, therefore, taken advantage of the characteristics of this new method to answer the question of whether central apneas, as defined by the classic and new methods, are accompanied by a critical narrowing of the airway, and at what time during the respiratory pause this occurs.

We designed this study to test the hypotheses that (*1*) a critical period of airway instability occurs early in the time course of some central apneas, and (*2*) maximal narrowing of the airway lumen occurs a few seconds after the initial decrease in airway diameter.

METHODS

Subjects

The study population consisted of 42 preterm infants referred to our apnea laboratory for assessment of clinically significant apnea. These infants (birth weight 2,090 ± 242 g [mean ± SE], study weight 2,650 ± 265 g, gestational age 33 ± 1 wk, postnatal age 37 ± 8 d) were studied

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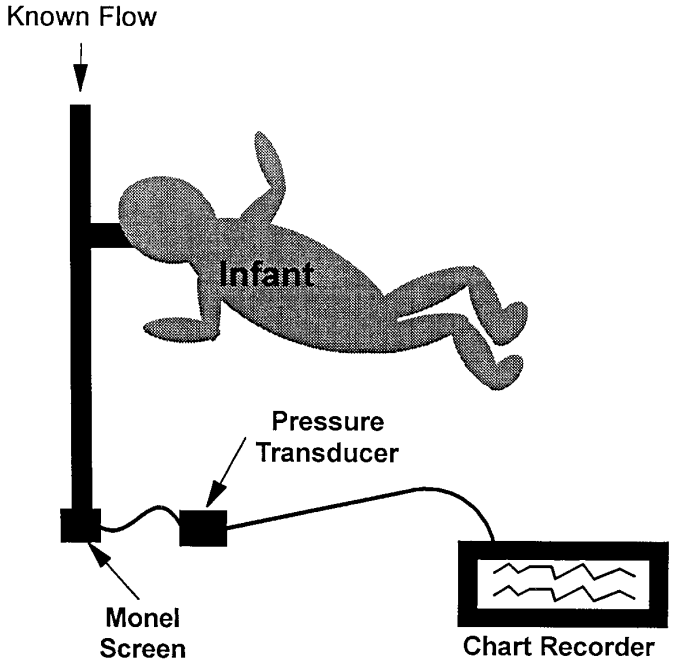

Figure 1. Diagram of the experimental system used to measure respiratory flow in infants. A known flow is passed down a tubing capped by a monel screen of fixed resistance. Alterations in transduced pressure is linearly related to changes in flow. When the background flow is electronically set to zero, alterations in the total flow produced by the addition or subtraction of flow by the infant result in deflections from the zero which is recorded on a chart recorder.

on 46 occasions. The birthweight range was 840 to 3,350 g; and the gestational age range was 25 to 35 wk. All subjects were breathing room air at the time of the study. The study was approved by the Faculty Committee for the Use of Human Subjects in Research at the University of Manitoba. Parental written consent was obtained.

Methods

Respiratory flow was measured using a nosepiece and a flow-through system as illustrated in Figure 1 (6, 7). The nosepiece was affixed to the face using tape, and a constant background flow of 3 L/min eliminated the need for valves in the system and thus reduced dead space. The background flow was set to an artificial zero and any gas added to (expiration) or withdrawn from (inspiration) this flow resulted in a deflection from zero. The screen flowmeter had a linear deflection up to 6 L/min and the resistance of the system is low (0.1 cm $H_2O \cdot L^{-1} \cdot min^{-1}$). During the studies, the electrocardiogram (EKG) was continuously monitored (Gould Biotach model #4307 13; Gould, Cleveland, OH) and was used to confirm beat to beat correlation of the EKG signal and the cardiac oscillations and exclude signals due to patient movement. Chest and abdominal excursions were detected through the use of mercury strain gauges (model 271 plethysmograph; Parks Electronic Lab, Beaverton, OR) placed at the level of the fourth intercostal space and just above the umbilicus. Variables were recorded on a polygraph (model 4221; Nihon Kohden, Tokyo, Japan). The flow signal was recorded on two channels, one of them amplified tenfold. Using this system oscillatory waveforms with flows $\geq$ 0.6 ml/s could be differentiated easily from background noise. Increasing gain above this level affected signal and noise equally and did not improve signal resolution.

Procedure

Infants were studied supine on an Ohio Neonatal Intensive Care Unit (Ohio Medical Instruments, Madison, WI) in our clinical laboratory located adjacent to the intermediate care nursery. A neutral thermal environment (abdominal skin temperature 36.5 $\pm$ 0.03° C) was maintained. No sedation was used. After appropriate placement of the nosepiece and electrodes for the EKG, infants were continuously monitored after falling asleep. When the infant did not settle, a feeding was offered. Similarly, if infants awoke during the study, they were fed and the study was continued.

Data Collection and Analysis

In the polygraphic tracing of these infants, all apneas $\geq$ 3 s were analyzed manually. Apneas were defined by absence of respiratory flow and deemed central if there were no respiratory efforts. We then inferred the degree of airway patency through the "presence or absence of cardiac oscillations on the magnified flow tracing" (5). For the present study only apneas with oscillation throughout were used. For each such apnea, the amplitude of the cardiac airflow oscillation was measured and converted to a percentage of the maximum amplitude observed in the infant's tracing to yield the relative amplitude. This allowed comparisons between infants of different sizes and lung compliances. For the subgroup of central apneas in which the amplitude of the oscillations was observed to decrease with time, apneas of varying durations were divided into 0.5 s intervals. In each apnea we determined the relative amplitude of the oscillation in each interval. Data so obtained from multiple apneas in multiple infants for each interval was pooled for analysis.

Statistical analysis consisted in using one-way analysis of variance to compare pooled data 0.5 s apart. For individual differences the Fisher's least significant difference test was applied. Values were expressed as mean $\pm$ SE. A probability value $\leq$ 0.05 was considered significant.

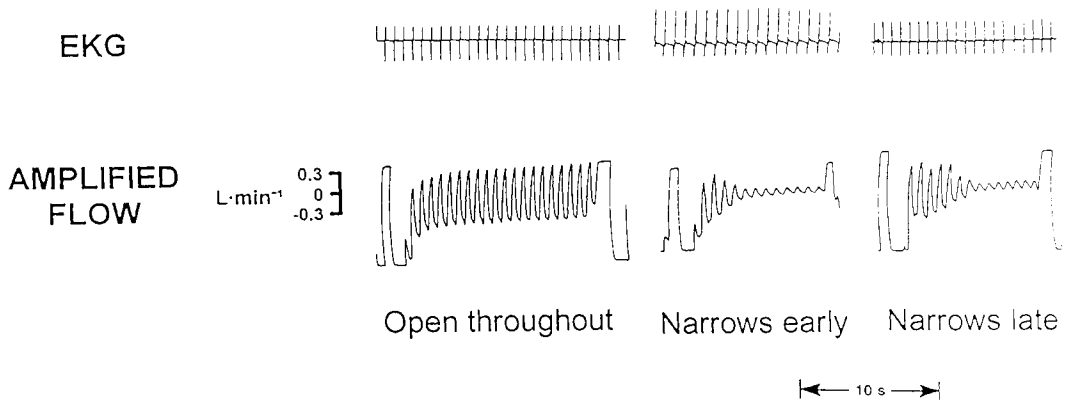

Figure 2. Three types of central apneas as defined by the continuous presence of oscillations. In one the presence of a uniform oscillation amplitude reflects maintained airway patency, while the remaining two tracings demonstrate airway narrowing taking place relatively earlier and later in the apnea.

RESULTS

General Observations

Forty six studies were performed in 41 preterm infants yielding 46 polygraphic recording. Each study lasted between 2 to 3 h. A total of 4,977 apneas ⩾ 3 s were analyzed using the new method, 4,456 (90%) apneas were central, 208 (4%) obstructive, and 313 (6%) mixed in type. Infants varied widely in the numbers of apneas with airway instability (four to 26 events), but there was a trend for smaller infants having greater instability.

Airway Instability

Of the 4,456 central apneas, 3,871 (87%) showed < 5% change in the amplitude of the cardiac oscillation during the apnea suggesting good airway patency. The remaining 585 (13%) apneas showed a decreasing amplitude of the cardiac oscillation suggesting narrowing of the airway (Figure 2). This latter group was analyzed to determine the timing of airway narrowing. Apnea duration in this subgroup ranged from 3 to 16 s. The data are summarized in Figures 3 and 4. There was no statistically significant difference between the initial (time = 0) and subsequent relative amplitudes until after 1 s had elapsed. All subsequent interval means were significantly different from the initial mean amplitude. This initial reduction in diameter 1 s into the apnea was similar for apneas of different lengths (Figure 4). Comparison of adjacent intervals using the Fisher's least significant difference test showed that there were significant differences from 1 to 8 s, but not afterwards. This indicates that in these apneas, the maximal degree of airway narrowing observed takes place over the first 9 s.

DISCUSSION

We have used a newly developed method of classifying types of apnea in preterm infants, based on the transmission of a cardiac oscillation signal when the airway is patent, to discover whether there is a critical period of airway instability during central apneas. We found that (*1*) there is a period of airway instability appearing approximately 1 s after the onset of apnea, (*2*) this critical period is similar for apneas of different durations, and (*3*) maximal narrowing of the airway lumen always occurs a few seconds after the critical period, usually within 9 s of the onset of apnea. These findings suggest that in a significant number of central apneas (13% in our study) there is a critical period of airway instability followed by airway narrowing. We speculate that this narrowing is due to loss of tone of upper airway musculature during apnea, and possibly also to the intrinsic pliability of the infant's cartilaginous supportive structures (8–13).

In earlier studies, apneas in preterm infants had been considered a central event (6). Only in subsequent years did it become clear that obstruction of the airways was frequently present (3, 12, 14, 15). Apneas have since been classified into central, obstructive, and mixed. Obstructive apneas are rare and are more frequently associated with movements (16).

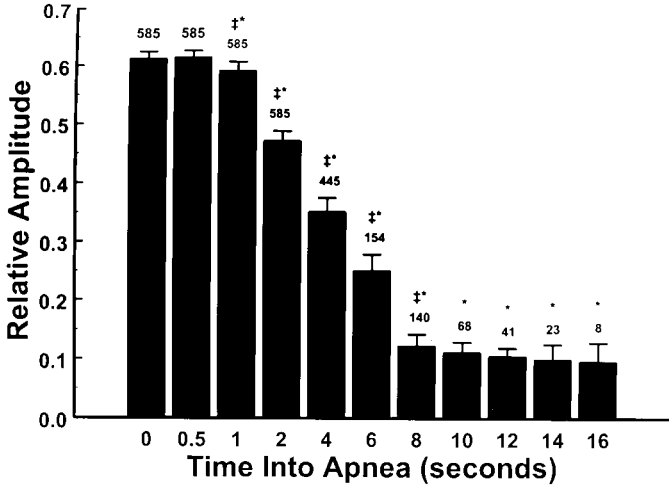

Figure 3. Changes in the relative amplitude of the cardiac oscillations over time for all apneas studied. Note that the mean relative amplitude becomes significantly different after 1 s and that the maximum airway narrowing takes place between 1 and 8 s into the apneas. Furthermore observe that the relative amplitude is not 1.0 at 0 s because in some apneas the initial amplitude is less than the maximal airway lumen diameter observed in the patient's entire tracing. Values are mean ± SE; *p ⩽ 0.05 compared with Time 0; ‡p ⩽ 0.05 compared with the preceding time interval.

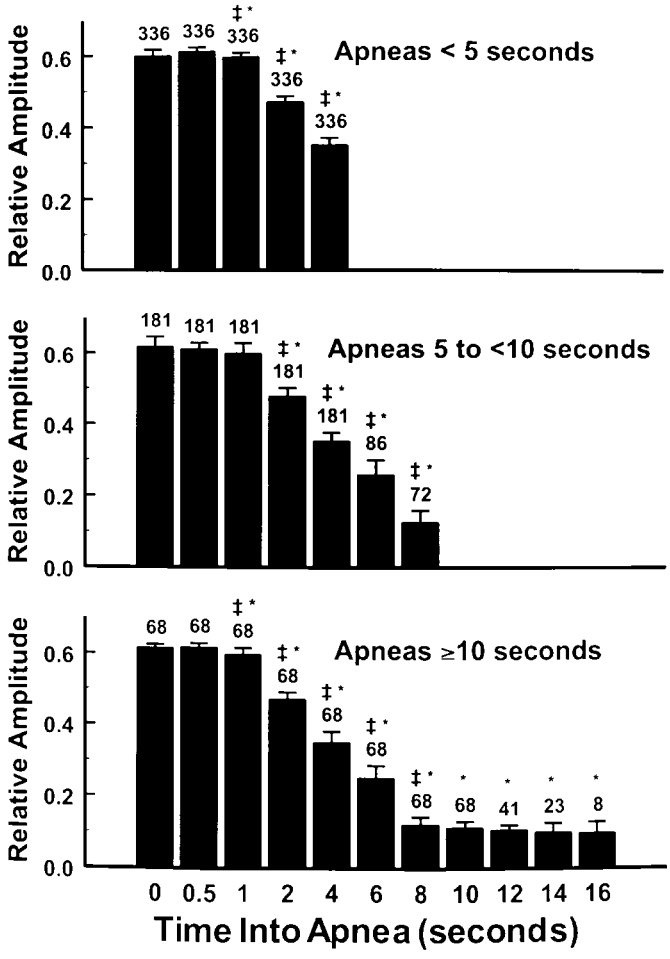

Figure 4. Changes in relative amplitude of the cardiac oscillations over time for apneas of different durations. Note that the critical period of maximum narrowing occurs at the same time despite different lengths. Furthermore observe that the relative amplitude is not 1.0 at 0 s because in some apneas the initial amplitude is less than the maximal airway lumen diameter observed in the patient's entire tracing. Values are mean ± SE with number of apneas shown above each data bar: *p ⩽ 0.05 compared with Time 0; ‡p ⩽ 0.05 compared with the preceding time interval.

Mixed apneas usually begin as a central event and then obstruct. Definition of obstruction has been traditionally made by the presence of respiratory efforts, usually abdominal and chest movements or diaphragmatic activity, in the absence of respiratory flow. Central apneas, however, were thought not to obstruct, as respiratory efforts were absent. Different studies have contradicted this assumption. By examination of the patency of the upper airway, either via direct visualization (bronchoscopy) or measuring the point in the tidal cycle where apnea starts, it has been shown that obstruction may also be present during central apneas (3, 4, 14). These observations raised many new questions: (*1*) How complete is this airway closure during central apnea? (*2*) Is there a critical period of airway instability? (*3*) What is the exact timing of airway narrowing during these apneas? None of these questions could be answered with the traditional method of assessing airway obstruction; however, a method based on the magnified cardiac oscillation appeared highly suitable, since the presence of oscillation is a function of airway patency and the amplitude of the oscillation is a real time measure of airway diameter. We have illustrated the merits of this technique by showing in the present study that in a subgroup of central apneas, there is a critical window of airway vulnerability at about 1 s into the apnea, followed by pronounced airway narrowing in the subsequent seconds.

We cannot compare our results on the instability of the airway with others in the literature because no other data are available. Milner and coworkers have used an unamplified cardiac oscillation signal to examine obstruction (3, 17). We have determined, however, that the unamplified tracing is frequently unable to detect the cardiac oscillation signal (5). Thus, the method reports more obstructions than are really present (5). We found that only the amplified oscillation can reliably detect patency of the airways (5). Figure 2 shows central apneas with a decrease in amplitude down to a plateau toward the end of apnea. That plateau would likely have been read as a straight line, and have been reported as an obstruction using the nonamplified method. This clearly illustrates the need for a highly discriminating method to define obstructive events in the airway. The magnified oscillation method appears to have these characteristics.

With the magnified method, the amplitude of the cardiac airflow oscillation should be proportional to the driving pressure provided by cardiac movement (18). In infants, cardiac output is primarily influenced by increases in heart rate and not stroke volume (19). Thus it is reasonable to assume that there will be little change in the magnitude of the cardiac airflow oscillation over time in infants. The amplitude of the transmitted oscillations should also be affected by the resistance of the airways within the thorax and the compliance of the chest wall itself, all of which will vary between patients. This is of particular importance in our patient population where varying degrees of bronchopulmonary dysplasia are common. These factors were taken into consideration with our analysis by describing the transmitted oscillation amplitude in terms of a relative amplitude (that is the ratio of the observed amplitude to the maximum amplitude observed in a particular study). Consequently, each infant served as its own control.

Although we have been able to determine the time of airway vulnerability during central apneas in preterm infants, the intrinsic mechanism and site of narrowing involved remains unknown. Although some authors have demonstrated active laryngeal adduction during central events, these apneas were not spontaneous but induced by barbituates or hypocapnea (20, 21). It has been suggested that a loss of tone of the upper airway musculature combined with early diaphragmatic contraction is a plausible mechanism for obstructions during obstructive and mixed apneas (22). The diaphragm would be asynchronous with the upper airway, would suck the airway in, and lead to complete obstruction. Such apneas are of much longer duration (23) than the events that we describe in this paper, leading to the speculation that in the apneas we have examined, respiratory efforts may have resulted in a reopening rather than the complete occlusion of the airway. Although this mechanism may indeed be present in many instances, we have shown in our previous paper that many apneas with late obstruction and complete disappearance of the cardiac oscillations are frequently not associated with diaphragmatic contractions (5). This means that the diaphragmatic contraction or its asynchrony with upper airway muscle action is not necessary to induce obstruction. The present findings reinforce this view as the airway has narrowed to near occlusion without any diaphragmatic action. It is more likely that the fundamental component of airway obstruction is really a loss of tone of the upper airway muscles with collapse. Why this occurs in only a percentage of the central apneas remains to be answered.

The use of the new method has proved to be a valuable tool in the noninvasive investigation of obstruction in neonatal apnea. However, further study is needed before advocating widespread application of the new method instead of the classical classification of apnea. Although it is tempting to favor the more simplified and direct methodology offered by the new method, it is possible that such a classification may disregard important factors in the complex pathophysiology of apnea. While the consequences of silent obstructions has yet to be studied, our findings have important clinical implications in the treatment of infant apnea. Current management centers on treating central apneas with stimulants such as methylxanthines and doxapram, while obstructive apneas are treated with positive distending pressure. It is apparent, however, that such treatment is directed at only the extremes of a spectrum of apneas, although most neonates have mixed events. Unfortunately the traditional classification of neonatal apnea is unable to detect obstruction without the presence of respiratory efforts. Moreover, it cannot determine if an infant has a lax airway and is prone to obstruction. We speculate that such information will be useful in guiding therapy and reducing the side effects associated with use of inappropriate treatment modalities, and this is a current focus of investigation in our laboratory.

In summary, we have examined a subgroup of central apneas in which the airway narrows as evidenced by the attenuation of a cardiac oscillation signal in the flow tracing. We found that there is a critical period of airway instability at about one second into the apnea and that the decrease in airway diameter reaches its maximum a few seconds after this critical period. The findings suggest the presence of a critical instability of the airway early in the apnea. The most likely mechanism for this appears to be loss of tone of upper airway musculature.

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