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Polysomnographic Determinants of Nocturnal Hypercapnia in Patients with Sleep Apnea

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SCIENTIFIC INVESTIGATIONS

Study Objectives: Identify polysomnographic and demographic factors associated with elevation of nocturnal end-tidal CO_2 in patients with obstructive sleep apnea.

Methods: Forty-four adult patients with obstructive sleep apnea were selected such that the maximal nocturnal end-tidal CO_2 was below 45 mm Hg in 15 studies, between 45 and 50 mm Hg in 14, and above 50 mm Hg in 15. Measurements included mean event (i.e., apneas or hypopneas) and mean inter-event duration, ratio of mean post- to mean pre-event amplitude, and percentage of total sleep time spent at an end-tidal CO_2 < 45, 45-50, and > 50 mm Hg. An integrated nocturnal CO_2 was calculated as the sum of the products of average end-tidal CO_2 at each time interval by percent of total sleep time spent at the corresponding time interval.

Results: The integrated nocturnal CO_2 was inversely correlated with mean post-apnea duration, with lesser contributions from mean apnea duration and age (R^2 = 0.56), but did not correlate with the apnea-hypopnea index, or the body mass index. Mean post-event to mean pre-event amplitude correlated with mean post-apnea duration (r = 0.88, p < 0.001). Mean apnea duration did not correlate with mean post-apnea duration.

Conclusions: Nocturnal capnometry reflects pathophysiologic features of sleep apnea, such as the balance of apnea and post-apnea duration, which are not captured by the apnea-hypopnea index. This study expands the indications of capnometry beyond apnea detection and quantification of hypoventilation syndromes.

Keywords: Obstructive sleep apnea, hypercapnia, capnography, body mass index, obesity hypoventilation syndrome

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Transcutaneous or end-tidal capnometry is commonly used in the polysomnographic evaluation of children in whom sleep disordered breathing manifests predominantly as obstructive hypoventilation.[1] Alternatively, the role of capnometry in adult polysomnography has been more limited, usually for the quantitative assessment of sleep hypoventilation syndromes,[2] or even less commonly, for the measurement of end-tidal CO_2 ($ETCO_2$) as an adjunct signal for the detection of airflow obstruction in sleep apnea.[3,4] Few studies are available to assess the use or accuracy of capnometry for those purposes,[5] and it therefore has not been routinely used in adult sleep laboratories.

However, current $ETCO_2$ sampling devices are reliable and only slightly underestimate the arterial CO_2, with a gradient of 5 mm Hg in patients with minimal ventilation-perfusion mismatch.[6] In obese postoperative patients with obstructive sleep apnea, the mean arterial to $ETCO_2$ gradient was 8.3 mm Hg.[7] Even in patients with diverse neuromuscular and pulmonary disorders, the $ETCO_2$ during sleep was found to underestimate a simultaneous arterial CO_2 by ≥ 10 mm Hg in only 21% of the readings.[8]

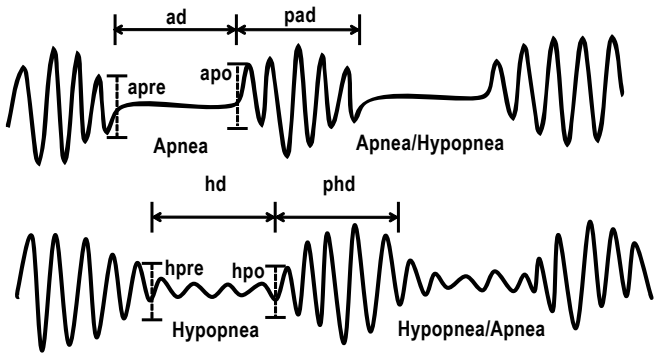
In that context, in patients with sleep apnea but without suspected sleep-hypoventilation syndromes, we noted elevation of nocturnal $ETCO_2$ that were unexpected in relation to the body mass index or the apnea-hypopnea index, indices usually associated with daytime hypercapnia in the obesity hypoventilation syndrome.[9] We therefore sought to determine whether the nocturnal $ETCO_2$ could reflect physiologic characteristics of obstructive sleep apnea not addressed by the apnea-hypopnea index or body mass index, and therefore expand its indication beyond the hypoventilation syndromes. For instance, contributors to the development of an elevated daytime arterial CO_2

BRIEF SUMMARY

Current Knowledge/Study Rationale: Although end-tidal CO_2 determination is reliable and accurate, its current application in polysomnography has been limited to the evaluation of sleep disordered breathing in children, the quantitative assessment of sleep hypoventilation syndromes, or as an adjunct signal for detection of sleep apnea. The aim of our study was to investigate whether end-tidal CO_2 is associated with polysomnographic or demographic characteristics in patients with sleep apnea.

Study Impact: Daytime and nocturnal end-tidal CO_2 are significantly related to post apnea duration, and to a lesser extent to apnea duration and age, but not to the apnea-hypopnea index or the body mass index. End-tidal CO_2 monitoring can therefore be expanded beyond its current applications in apnea detection and hypoventilation syndromes, to its use as a marker of the pathophysiology, severity, and ventilatory burden of sleep apnea, all features that may be inadequately captured by the apnea-hypopnea index.

Figure 1—Schema illustrating event and inter-event duration, as well as pre-and post-event amplitude (with upward deflection of flow during inspiration)



Inter-event durations were included only if the subsequent respiratory event was within 30 sec from the termination of the preceding event. ad: apnea duration, pad: post apnea duration, hd: hypopnea duration, phd: post-hypopnea duration, apre and apo: pre- and post-apnea amplitude respectively, hpre and hpo: pre- and post-hypopnea amplitude, respectively. For each patient the mean of all event and inter-event durations across the polysomnography was derived and expressed in the text or tables as AD, PAD, HD, and PHD. Similarly, the mean of all pre-event amplitude and the mean of all post-event amplitudes was derived and expressed in the text as Apre, Apo, Hpre, and Hpo.

linked to obstructive respiratory events during sleep include post-event (subsuming apneas and hypopneas) ventilation as a function of CO_2 load[10,11] and apnea duration in relation to post-apnea duration.[12]

We therefore selected groups of obstructive sleep apnea patients with different severity of nocturnal CO_2 elevation and assessed the relative contributions of demographic factors, sleep apnea severity, respiratory event and respiratory inter-event duration, as well as post-event amplitude relative to pre-event amplitude, to an overall measure of nocturnal $ETCO_2$.

METHODS

We reviewed polysomnograms and clinical charts of patients diagnosed with obstructive sleep apnea at our center from 2008 to 2009. Inclusion criteria were age > 18 years, total sleep time ≥ 6 h with a sleep efficiency ≥ 65%,[13] and an apnea-hypopnea index ≥ 5. We excluded studies where central apneas represented > 50% of the apnea-hypopnea index, studies requiring oxygen administration, titration studies, and other conditions that could confound the nocturnal CO_2 or impair the accuracy of the $ETCO_2$ as a measure of arterial CO_2 (i.e., chronic obstructive pulmonary disease, asthma, neuromuscular diseases, use of diuretics, alcohol or narcotics, or > 20 pack-year smoking history). To ensure an adequate representation of various ranges of CO_2 values, we aimed for an equal number of patients in each of the following groups: maximal nocturnal $ETCO_2$ < 45 mm Hg, between 45 and 50 mm Hg, and > 50 mm Hg.

All polysomnograms were recorded on Polysmith systems (Nihon Kohden, Foothill Ranch, CA), and scored using American Academy of Sleep Medicine guidelines.[2] Capnometry data were obtained from calibrated Nonin RespSense devices (Plymouth, MN) interfaced to the Polysmith system. Those devices use a sidestream technology, with sampling obtained through oral/nasal cannulas (Salter labs, Arvin, CA). The sampling flow into the sample cell was 75 mL/min, the total system response time (including delay and rise times) was 4 sec, and the sampling rate for the capnograph tracing was 4 Hz. Apnea was defined as a drop in the peak thermal sensor excursion by ≥ 90% from baseline lasting ≥ 10 seconds. For the purpose of this study, a hypopnea was scored if the event met either the recommended or alternative definitions of the American Academy of Sleep Medicine (i.e., a drop in the nasal pressure signal excursion ≥ 30% from baseline for ≥ 10 sec in association with ≥ 4% oxygen desaturation, or ≥ 50% drop with ≥ 3% desaturation or an arousal).[2]

The quality of the oximetry and capnographic data was assessed by review of the pulse plethysmographic signal and capnographic waveforms, with exclusion of artifacts of oximetry due to loss of the pulse signal, and exclusion of CO_2 waveforms without a clearly identified plateau, including those associated with deterioration of the signal due to obstructive events.

We collected demographic and polysomnographic variables at the time of the PSG: age, sex, body mass index, Epworth Sleepiness Scale score, sleep efficiency, sleep and REM latencies, sleep stage distribution, arousal index, apnea-hypopnea index, nadir oxygen saturation, and time spent below 90% oxygen saturation (as percent of total sleep time). Capnometric data were obtained from the trend report of the Polysmith system, and included stable awake end-tidal CO_2 at the beginning of the study before the onset of slow-rolling eye movements (evening awake $ETCO_2$), after completion of the sleep study just before the final calibrations (morning awake $ETCO_2$), and sleep $ETCO_2$. The latter included minimum and maximum sleep $ETCO_2$ and the following 3 time intervals: percents of total sleep time spent with $ETCO_2$ < 45 mm Hg (T45), between 45-50 mm Hg (T45_50), and > 50 mm Hg (T50). An integrated overnight CO_2 was calculated as the sum of the products of the estimated average $ETCO_2$ at each of those 3 time intervals by the percent of total sleep time spent at each corresponding time interval: [T45*(45 + minimum $ETCO_2$) / 2] + [T50*(50 + maximum $ETCO_2$) / 2] + [T45_50 *47.5]. The result was divided by 100 to provide an estimate of nocturnal $ETCO_2$ had it remained constant through the night.

Respiratory event (subsuming apneas and hypopneas) and inter-event durations were measured in seconds. Inter-event durations were measured only if the subsequent respiratory event was within 30 sec from the termination of the preceding event. Pre-event and post-event breathing amplitudes were semi-quantitatively measured on the nasal pressure transducer signal on 60-sec epochs, as the amplitude of the last breath before the corresponding respiratory event and of the first breath after that event respectively (**Figure 1**). To compensate for expected variation in amplitudes as may occur with positional changes or migration of the oral/nasal cannula, the mean post-event amplitude was referenced to the mean pre-event amplitude.

The onset and offset of apneas and hypopneas were respectively placed at the nadir of the last normal breath and at the start of the first subsequent normal breath approximating the baseline (**Figure 1**).[2] If the baseline amplitude could not be easily determined, the respiratory events were also terminated as per the American Academy of Sleep Medicine guidelines when

Table 1—Demographic, laboratory, and polysomnographic variables at baseline

	Maximal sleep end-tidal CO_2 (mm Hg)				
	< 45	45-50	> 50	Mean	p-value*
Age (years)	49 (14)	53 (16)	51 (12)	51 (14)	0.74
Gender (F/M)	8/7	9/5	7/8	24/20	0.63†
Body mass index (kg/m^2)	30 (7)	36 (7)	36 (10)	34 (9)	0.12
Neck circumference (cm)	37 (5)	41 (5)	42 (5)	40 (5)	< 0.05‡
Epworth	12 (6)	10 (4)	11 (4)	11 (5)	0.53
Apnea-hypopnea index (events/h)	22 (13)	30 (22)	34 (27)	28 (21)	0.36
Nadir O_2 sat (%)	83 (8)	82 (6)	80 (9)	82 (8)	0.55
% time with SO_2 < 90%	3 (4)	15 (23)	10 (16)	9 (17)	0.12
Maximal end-tidal CO_2 (mm Hg)	40.1 (9.2)	48.1 (1.6)	57.0 (7.2)	48.4 (9.8)	< 0.001
Awake evening end-tidal CO_2 (mm Hg)	34.5 (3.8)	40.5 (2.9)	46.6 (3.7)	40.6 (6.1)	< 0.001
Arousal index (events/h)	26.6 (9.8)	31.5 (16.9)	33.2 (25.6)	30.5 (18.4)	0.61
Percent supine (%)	42.1 (23.0)	35.1 (26.5)	53.5 (36.4)	43.8 (29.7)	0.24
Stage N3 sleep (%)	9 (9)	13 (12)	10 (12)	11 (11)	0.62
Stage REM sleep (%)	17 (7)	17 (8)	12 (7)	15 (7)	0.12

Values expressed as mean (standard deviation) except for gender row. *One way analysis of variance unless otherwise indicated; †χ^2 test; ‡By contrast analysis, neck circumference in the combined groups with Max $ETCO_2 \geq 45$ mm Hg was higher vs. the group with Max $ETCO_2 < 45$ mm Hg ($p < 0.02$).

there was a clear and sustained increase in post-event breathing amplitude, or re-saturation of ≥ 2%.[2]

For each patient we derived: mean apnea and mean hypopnea duration (AD and HD respectively), mean post-apnea and mean post-hypopnea duration (PAD and PHD), mean post-apnea and mean post-hypopnea amplitude (Apo and Hpo) expressed relative to the mean pre-apnea and mean pre-hypopnea amplitude (Apre and Hpre).

Sample size was estimated at 30 subjects based on a minimum meaningful correlation coefficient of 0.50, a power of 0.9, and α of 0.05.[14] Groups were compared using a χ^2 for categorical variables, and analysis of variance for continuous variables. The correlation between integrated overnight CO_2 and demographic and polysomnographic variables was determined by the Pearson correlation coefficient. Comparison of correlations within a single sample was done using the Williams T_2 statistic.[15] Multiple linear regression analysis was performed to estimate the influence of covariates on the overnight CO_2. Collinearity was measured by means of tolerance and the Variance Inflation Factor. Statistical significance was set at $p < 0.05$. Analyses were performed using SPSS, version 11.5. The study was approved by our institutional review board.

RESULTS

Forty-four consecutive studies meeting the inclusion criteria were selected such that maximal $ETCO_2$ during sleep was < 45 mm Hg in 15 studies, between 45 and 50 mm Hg in 14 studies, and > 50 mm Hg in 15 studies. The mean age of the patients was 51 years (standard deviation 14, range 18-92), mean apnea-hypopnea index was 28 events/h (standard deviation 21, range 5.1-105), and the mean body mass index was 34 kg/m^2 (standard deviation 9, range 20-57). There were 24 females and 19 males. None had a diagnosis of obesity-hypoventilation. There were no significant differences between genders in the body mass index, apnea-hypopnea index, mean apnea duration, mean post-apnea duration, and mean post-event to mean pre-event ventilation, though women tended to be older than men (54 vs. 47 years, respectively, $p = 0.06$), and to have a smaller neck circumference (38.7 vs. 41.4 cm, respectively, $p = 0.07$).

Demographic, polysomnographic, and laboratory data categorized by level of maximal $ETCO_2$ reached during the sleep study are shown in **Table 1**. Neck circumference was higher in the combined groups with maximal $ETCO_2 \geq 45$ mm Hg compared to the group with maximal $ETCO_2 < 45$ mm Hg (**Table 1**). Sleep efficiency, percentages of time spent at different sleep stages, percent of time in the supine position, arousal indices, and sleep and REM latency were not significantly different between the 3 groups.

Groups with progressively higher maximal $ETCO_2$ had progressively shorter mean post-apnea duration, increased AD/PAD, and a smaller mean post-event to mean pre-event amplitude ratio (**Table 2**).

There was a trend towards a positive correlation between the integrated overnight CO_2 and age ($r = 0.29$, $p = 0.06$), as well as body mass index ($r = 0.29$, $p = 0.06$), and no significant correlation with apnea-hypopnea index, neck circumference, Epworth Sleepiness Scale score, sleep efficiency, sleep stages, percent time in the supine position, and percent time with oxygen saturation < 90%.

The REM latency correlated negatively with mean post-apnea duration ($r = -0.41$, $p = 0.006$), whereas REM time as percent of total sleep time correlated positively with the mean post-apnea duration ($r = 0.34$, $p = 0.03$).

The integrated overnight CO_2 correlated with mean apnea duration ($r = 0.41$, $p = 0.005$) (**Figure 2A**), and mean-post apnea duration ($r = -0.67$, $p < 0.001$) (**Figure 2B**). The correlation of the integrated overnight CO_2 with mean hypopnea duration or mean post-hypopnea duration was very poor and nonsignificant ($r = -0.10$, $p = 0.53$ and $r = 0.11$, $p = 0.50$, respectively). There was no difference between apnea and hypopneas as far as the correlation between the integrated overnight CO_2 and the post-

Table 2—Comparison of possible variables predictive of end-tidal CO_2 during sleep

	Maximal Sleep end-tidal CO_2 (mm Hg)				
	< 45	45-50	> 50	Mean	p-value*
Mean Apnea Duration: AD (s)	10.70 (0.82)	12.64 (1.39)†	12.04 (1.35)†	11.79 (1.45)	< 0.001
Mean Post-Apnea Duration: PAD (s)	19.82 (1.61)	17.89 (1.60)†	11.07 (2.10)†‡	16.44 (3.99)	< 0.001
AD/PAD	0.54 (0.05)	0.71 (0.10)†	1.13 (0.28)†‡	0.78 (0.28)	< 0.001
Mean Hypopnea Duration: HD (s)	12.00 (1.43)	11.38 (1.42)	12.23 (1.49)	11.87 (1.46)	0.28
Mean Post-Hypopnea Duration: PHD (s)	10.42 (2.92)	18.62 (26.91)	12.60 (1.43)	13.80 (15.49)	0.35
HD/PHD	1.26 (0.45)	1.02 (0.48)	0.98 (0.15)	1.09 (0.40)	0.12
Mean Post- to Mean Pre-Apnea Amplitude: Apo / Apre	1.65 (0.29)	1.13 (0.13)†	0.67 (0.16)†‡	1.41 (0.42)	< 0.001
Mean Post- to Mean Pre-Hypopnea Amplitude: Hpo / Hpre	1.52 (0.25)	1.03 (0.13)†	0.57 (0.13)†	1.28 (0.32)	< 0.001
Event amplitude ratio: (Apo + Hpo) / (Apre + Hpre)	1.57 (0.15)	1.08 (0.12)†	0.62 (0.13)†‡	1.09 (0.42)	< 0.001

Values expressed as mean (standard deviation). *By multivariate analysis of variance. †Represents significant difference compared to Max $ETCO_2$ < 45 mm Hg group by contrast analysis. ‡Represents significant difference compared to Max $ETCO_2$ 45-50 mm Hg group by post hoc analysis.

Table 3—Multiple regression of post-apnea duration, apnea duration, and age as predictors of the integrated overnight CO_2

Parameter	Coefficient	p-value	R^2
Post-Apnea Duration: PAD (s)	-0.65	< 0.001	0.45
Apnea Duration: AD (s)	0.87	0.02	0.06
Age (years)	0.08	0.04	0.05

Integrated overnight CO_2 = 36.2 – (0.65*PAD) + (0.87*AD) + (0.08*Age). (Model R^2 = 0.56).

event relative to pre-event amplitude, with comparable correlation coefficients (p = 0.30), slopes, and intercepts. Therefore a mean post-event to mean pre-event (combining apneas and hypopneas) amplitude ratio was calculated, with which the integrated overnight CO_2 was also correlated (r = -0.71, p < 0.001) (**Figure 2C**).

The evening and morning awake $ETCO_2$ were nearly identical and closely correlated (40.7 ± 6.2 vs. 40.5 ± 5.8 mm Hg, respectively; r = 0.81, p < 0.001). The evening awake $ETCO_2$ correlated positively with mean apnea duration (r = 0.42, p = 0.004), inversely with mean post-apnea duration (r = -0.81, p < 0.001), and inversely with mean post- to mean pre-event amplitude ratio (r = -0.80, p < 0.001).

Cross-correlation analysis indicated that collinearity was a concern, as the mean post-event to mean pre-event amplitude ratio was correlated with mean apnea duration (r = -0.43, p = 0.005), and particularly with mean post-apnea duration (r = 0.88, p < 0.001) (**Figure 3**). However, mean post-apnea duration was not correlated with mean apnea duration (r = -0.25, p = 0.10).

In a multivariable regression model, mean post-apnea duration, mean apnea duration, and age were each independently correlated with the integrated overnight CO_2: mean post-apnea duration contributing the most to the variance in integrated overnight CO_2 (45%), with mean apnea duration and age contributing an additional 6% and 5%, respectively, such that the total model explained 56% of the variance in integrated overnight CO_2 (**Table 3**). The body mass index and apnea-hypopnea index were not significantly correlated with the integrated overnight CO_2 in the multivariable model (p = 0.17 and 0.47, respectively).

DISCUSSION

Our study shows that, in patients with obstructive apnea: (1) A shorter post-apnea duration is a greater contributor to an elevated integrated overnight CO_2 than apnea duration, with older age as an additional lesser contributor; (2) Post-hypopnea amplitude is equally as important as the post-apnea amplitude with post-event relative to pre-event (combining apneas and hypopneas) amplitude contributing to the integrated overnight CO_2, but also correlating strongly with apnea duration and post-apnea duration; (3) Post-apnea duration is not correlated with apnea duration; (4) The apnea-hypopnea index, body mass index, hypopnea duration, and post-hypopnea duration are not important contributors to the overnight CO_2; and (5) The baseline awake end-tidal CO_2 also correlated positively with mean apnea duration, and inversely with mean post-apnea duration and post-event amplitude relative to pre-event amplitude.

In our study, the post-event to pre-event amplitude ratio was tightly correlated with post-apnea duration (**Figure 3B**), suggesting that a common pathophysiologic mechanism, possibly airway collapsibility, underlies those two measures, and may explain our finding of an association between longer post-apnea duration and a more favorable REM architecture (with both a shorter REM latency and increased REM sleep). For instance, stable breathing correlated with passive collapsibility of the airway in patients with suspected obstructive sleep apnea.[16] Consequently, multi-collinearity was seen between post-apnea duration and post-event to pre-event amplitude. Although ventilatory measures such as breath amplitude may be as important as post-apnea duration, the individual contribution of each of those two variables to the overnight integrated CO_2 is difficult to discern in the context of collinearity. We therefore included only the apnea and post-apnea durations in the final model shown in **Table 3**, because durations were more sharply defined, less subject to variability in measurements (compared to amplitudes), limited to apneas (and therefore independent of the various hypopnea definitions), and independent of correc-

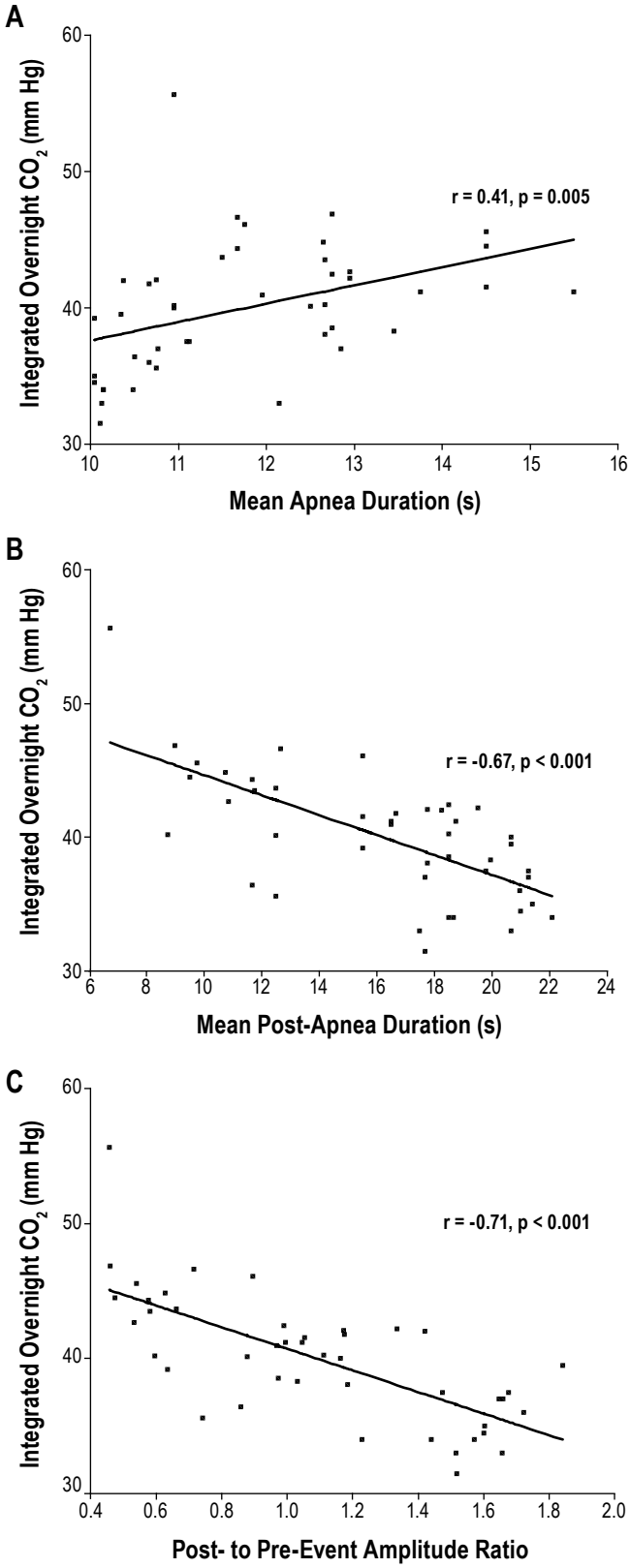
tion measures (such as square root modification of the nasal pressure amplitude signal[17,18]) to compensate for the nonlinear nasal pressure to flow relationship.

However, once the airway has collapsed and an apnea or hypopnea begun, the duration of the obstructive events may depend on factors other than collapsibility such as the arousal threshold. For instance, since arousals terminate an obstructive event, apnea duration has been considered a surrogate of the arousal threshold.[19] These proposals, with separate determinants of apnea duration and post-apnea duration, are consistent with the absence of an inverse correlation between those two variables in our study as well as other studies.[12]

The integrated overnight CO_2, did not correlate with hypopnea and post-hypopnea durations, perhaps reflecting the shape of the relationship between CO_2 and ventilation (the metabolic hyperbola), such that the reduced ventilation during hypopneas, was either sufficient to prevent an increase in arterial CO_2, or decreased our ability to detect such an effect within the technical constraints of our study. In that regard, the most important constraint is our removal of data associated with deterioration of the capnographic waveforms during obstructive events. This may have resulted in an underestimation of the true overall nocturnal CO_2, and perhaps explain why apnea duration was not as strong a predictor of nocturnal CO_2 as post-apnea duration in our study (an alternative explanation may be the constraint of the conventional 10-second threshold to the apnea definition). Note that loss of the capnographic signal during obstruction, which is considered an artifact in our study, has been used diagnostically to detect apneas,[3] such that the lowered overnight end-tidal CO_2, was shown to be associated with the apnea-hypopnea index severity.[4]We confirm the results of other studies showing a relationship between a longer apneas or shorter post-apnea duration with a higher awake arterial CO_2,[12,20] and between an impaired post-event ventilatory response and a higher awake arterial CO_2.[10,11] Our study extends those results and demonstrates that, in individuals with obstructive sleep apnea, gradations of the awake CO_2 even within the normal range, reflect events occurring during sleep, with elevation of nocturnal carbon dioxide as a possible intermediary step associated with shorter post-apnea duration, with lesser contributions from longer apnea duration, and increased age.

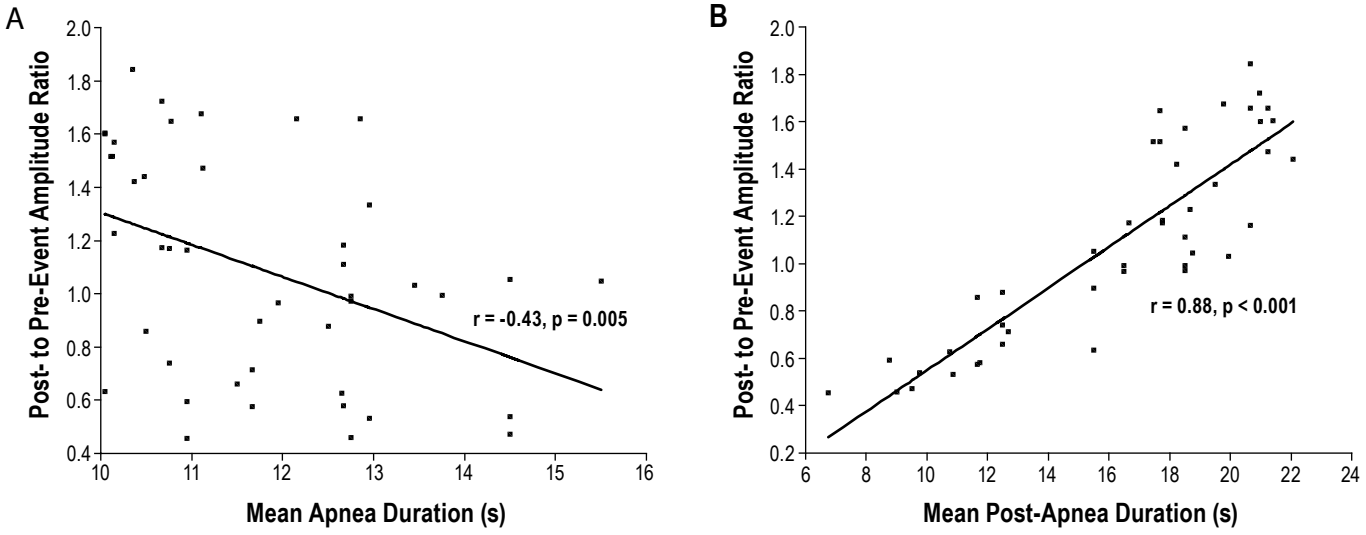
In contrast, we found that the apnea-hypopnea index was not a significant predictor of the integrated overnight CO_2, and that the body mass index trended towards a poor correlation with the integrated overnight CO_2, though both are important determinants of daytime hypercapnia in obese patients with obstructive sleep apnea.[9] A potential explanation for those findings is that, beyond causing variations of awake CO_2 within the normal range, inciting events to nocturnal hypercapnia (such as lower post-event ventilation, longer apnea duration, shorter post-apnea duration) require other factors (such as the apnea-hypopnea index or body mass index) for the transition to daytime hypercapnia. For instance, obese patients, and especially those with the metabolic syndrome, have a higher resting metabolic rate compared to non-obese patients[21,22] but also have a decrease in metabolic rate during sleep in direct proportion to the body mass index.[21] The resting to sleep differential in the metabolic rate based on body mass index, may explain the stronger contribution of

Figure 2—Scatter plots of the integrated overnight CO_2 against mean apnea duration **(A)**, mean post-apnea duration **(B)**, and mean post-to mean pre-event amplitude ratio **(C)**, with regression line, correlation coefficient, and significance



Each point represents one patient.

Figure 3—Scatter plots of the mean post-event amplitude to mean pre-event amplitude ratio against mean apnea duration **(A)**, and mean post-apnea duration **(B)**, with regression line, correlation coefficient, and significance



Each point represents one patient.

the body mass index to the development of daytime as opposed to nocturnal hypercapnia.

Our findings do not establish whether an impairment of ventilation (as determined by apnea and post-apnea duration, or post-ventilation relative to pre-ventilation) determines $ETCO_2$, or whether elevation in the $ETCO_2$ impairs ventilation. However, progressive hypercapnia above a certain threshold improves upper airway stability in a linear fashion.[23-25] This pharyngeal chemosensitivity parallels the control gain of central and peripheral chemoreceptors, with the net effect that increased CO_2 protects and increases ventilation. Our findings are therefore more consistent with a ventilatory impairment in the balance between the accumulation of CO_2 (longer apnea duration) and perhaps more importantly the unloading of CO_2 (longer post-apnea duration) leading to nocturnal then daytime elevation of CO_2.

Our study expands the indications of capnometry during polysomnography beyond its current contexts of apnea detection and quantification of the hypoventilation syndromes[5] to its use as a reflection of the pathophysiology, severity, or ventilatory burden of sleep apnea, which may not be fully captured by the apnea-hypopnea index. These findings may have both diagnostic and prognostic clinical implications, as exhaled CO_2 may be a physiologic marker of disease severity that is independent of the apnea-hypopnea index, reflects the balance between event and inter-event duration, and may be an intermediary stage towards the development of daytime hypercapnia in some individuals. Advances in methods of exhaled breath analysis may broaden the role of exhaled CO_2 as a diagnostic tool and therapeutic target in patients with sleep apnea.[26]

ABBREVIATIONS

AD, mean apnea duration
Apo, mean post-apnea amplitude
Apre, mean pre-apnea amplitude
$ETCO_2$, end-tidal CO_2
HD, mean hypopnea duration
Hpo, mean post-hypopnea amplitude
Hpre, mean pre-hypopnea amplitude
PAD, mean post-apnea duration
PHD, mean post-hypopnea duration

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