Title

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Journal

The American Journal of Cardiology, 117(6)

ISSN

0002-9149

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Publication Date

2016-03-01

DOI

10.1016/j.amjcard.2015.12.035

Peer reviewed

Usefulness of Low Cardiac Index to Predict Sleep-Disordered Breathing in Chronic Thromboembolic Pulmonary Hypertension

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Patients with chronic thromboembolic pulmonary hypertension (CTEPH) often have substantial right ventricular dysfunction. The resulting low cardiac index might predispose to sleep disordered breathing (SDB) by increasing ventilatory instability. The prevalence of SDB and potential association with impaired cardiac index was examined in patients with CTEPH. Patients referred for evaluation for pulmonary thromboendarterectomy surgery were recruited. Subjects underwent a sleep study, unless already using positive airway pressure therapy. Hemodynamic data were obtained from contemporaneous right-sided cardiac catheterization. A total of 49 subjects were included. SDB—defined as ongoing positive airway pressure use or apnea-hypopnea index (AHI) ≥5/h—was found in 57% of subjects. SDB was generally mild in severity, with respiratory events mainly consisting of hypopneas. Cardiac index was found to be significantly lower in subjects with SDB than those without (2.19 vs 2.55 L/min/m^2; p = 0.024), whereas no differences were observed in other characteristics. Additionally, cardiac index was independently predictive of AHI. In a subgroup of subjects with an elevated percentage of central events, both cardiac index and lung to finger circulation time correlated with AHI. In conclusion, SDB is prevalent in patients with CTEPH and might decrease with treatments that improve cardiac index. **(Am J Cardiol 2016;117:1001−1005)**

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) have variable degrees of right ventricular dysfunction because of chronic blood clots and remodeling of the pulmonary vasculature leading to pulmonary hypertension. Patients with CTEPH may, therefore, have impaired cardiac index but typically lack elevated left-sided cardiac pressures. Sleep disordered breathing (SDB) is prevalent in patients with left-sided heart failure, with previous research suggesting this is because of elevated left heart filling pressures leading to increased chemosensitivity.[1−3] However, the independent effect of low cardiac output might additionally predispose to SDB, and therefore, patients with CTEPH may also be at risk.[4−7] To our knowledge, there is no dedicated study to examining SDB in CTEPH.[8−13] The aims of this study are

1. Characterize SDB in patients with CTEPH.
2. Examine the hypothesis that low cardiac index is predictive of SDB in this cohort of patients without left ventricular dysfunction.

Methods

Patients referred for evaluation for pulmonary thromboendarterectomy surgery were sequentially recruited for participation. Exclusion criterion was an expert clinician assessment that the etiology of pulmonary hypertension was not CTEPH. The institutional review board at the University of California San Diego approved the protocol. Written, informed consent was obtained from all subjects.

Enrolled participants underwent sleep testing with an ApneaLink Plus (ResMed, San Diego, California), consisting of nasal pressure sensor, respiratory effort band, and pulse oximeter worn on the finger. For safety of participants and consistency in baseline oxygenation, subjects on nocturnal supplemental oxygen were maintained on their prescribed setting, with the sensor placed above the oxygen cannula. Similarly, for safety of participants, subjects with a previous diagnosis of SDB actively using positive airway pressure (PAP) therapy were regarded as having SDB; no sleep study was performed.

Studies were scored by a blinded, registered polysomnographic technologist using modified American Academy of Sleep Medicine Chicago Criteria.[14] Specifically, apnea was defined as a >90% reduction in airflow and hypopnea defined as a >30% reduction in airflow, lasting >10 seconds, and associated with a ≥3% oxyhemoglobin desaturation. Obstructive apneas were associated with thoracic effort and/or associated flow limitation. Hypopneas were scored as undifferentiated events.

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Funding Sources: NIH/NHLBI T32 HL098062-05.

See page 1005 for disclosure information.

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0002-9149/16/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2015.12.035

Table 1
Prevalence, characteristics, and hemodynamics in subjects with and without sleep disordered breathing, all subjects (N = 49)

Variable	Sleep disordered breathing		P-value
	No 21 (43%)	Yes 28 (57%)	
		PAP use 10 (20%) AHI ≥ 5/h 18 (37%)	
Men	43%	57%	0.483
Age (years)	49.2 ± 3.9	54.9 ± 2.6	0.403
Body mass index (kg/m^2)	28 (23-34)	30 (26-34)	0.225
Sedative/narcotic use	29%	21%	0.811
Epworth sleepiness score (out of 24)	7 ± 0.95	9 ± 1.18	0.216
Mean pulmonary artery pressure (mmHg)	40 ± 2.4	46 ± 2.3	0.100
Pulmonary vascular resistance (dyne-s/cm^5)	513 ± 65	668 ± 66	0.108
Right atrial pressure (mmHg)	8 (5-12)	9 (5-16)	0.484
Pulmonary artery wedge pressure (mmHg)	10 (8-14)	11 (8-16)	0.879
Cardiac index (L/min/m^2)	2.55 ± 0.12	2.19 ± 0.10	**0.024**
Cardiac output (L/min)	5.14 ± 0.30	4.55 ± 0.25	0.140

Data presented as mean ± SEM, or medians (IQR).
Bold text denotes meeting pre-specified statistical threshold of P <0.05.

Subjects underwent right-sided cardiac catheterization as part of a standard clinical evaluation. Briefly, patients were brought into the catheterization laboratory and were measured while supine at rest. A Swan-Ganz catheter was advanced to the pulmonary artery under fluoroscopic guidance. With appropriate respiratory timing, right-sided pressures were transduced hydrostatically. Cardiac output was measured by thermodilution of room temperature saline.

Lung to finger circulation time (LFCT) has been previously described as a measure of circulatory delay in patients with SDB.[15,16] Flow and saturation waveforms from sleep study data were analyzed in Spike2 software (CED, Cambridge, UK). In a blinded fashion, all recordings were screened for scorable events, defined as having a distinct end of hypopnea/apnea with an associated desaturation of ≥3%. LFCT was measured from the end of a respiratory event to the onset of resaturation; 10 events from the start and 10 events from the end of the recording were selected. If <20 events were available, all events were used; however, subjects with <4 events were excluded from analysis. The mean LFCT for each subject was reported.

Analysis was performed using SigmaPlot (Systat Software Inc, San Jose, California) and SAS Studio (SAS Institute, Cary, North Carolina). Means were compared using a *t* test or rank-sum test, and proportions compared using a chi-square test. Pearson's product-moment or Spearman rank-order correlation was used as appropriate. Linear regression and logistic regression were performed with variables of interest. A p value <0.05 was considered statistically significant.

Table 2
Portable sleep testing data (N = 39)

Variable	Apnea-hypopnea index	
	< 5/h	≥ 5/h
Subjects (%)	21 (54%)	18 (46%)
Events/hour, Number of subjects		
5-15/h		10 (26%)
15-30/h		6 (15%)
>30/h		2 (5%)
Apnea-hypopnea index (events/h)	2.6	19.0 *
Obstructive apnea index (events/h)	0.3	4.6 *
Central apnea index (events/h)	0.2	0.9 †
Hypopnea index (events/h)	2.1	13.4 *
% Events obstructive apneas	14%	13% †
% Events central apneas	7%	4% †
% Events hypopneas	80%	82% †
Baseline SaO_2 (%)	92%	93% †
Time <90% SaO_2 (%)	42%	50% †
Nadir SaO_2	81%	80% †
Supplemental O_2 use (%)	54%	46% †

Data presented as mean ± SEM, or medians (IQR).
* P <0.001 compared to the AHI <5/h group.
† P >0.05 compared to the AHI <5/h group.

Results

Of 75 patients screened for inclusion, 19 declined, 3 did not have CTEPH, 2 had missing sleep study data, and 2 did not undergo cardiac catheterization. Thus, complete data were obtained in 49 subjects, all of whom had a diagnosis of CTEPH following clinical and radiographic evaluation by expert clinician consensus; 45 subjects subsequently elected to undergo pulmonary thromboendarterectomy surgery, allowing for pathologic confirmation of CTEPH.

The prevalence of SDB among 49 total subjects is reported in Table 1. Using a definition of SDB as either PAP use at enrollment or an apnea-hypopnea index (AHI) ≥5/h, the prevalence of SDB was 57%. Characterization of SDB found on sleep studies is reported in Table 2, revealing primarily mild SDB with events consisting primarily of hypopneas. There were no differences with respect to age, gender, body mass index (BMI), or sedative use between those with and without SDB (Table 1).

Of the 39 subjects not using PAP, 44% were using supplemental oxygen on enrollment. The percentage of subjects using oxygen did not differ between those with and without SDB on sleep studies (Table 2). There was no significant difference in the AHI between those using oxygen and those who were not (6 vs 13 events/h; p = 0.229). Similarly, no significant difference was found between the 2 groups with respect to baseline saturation (94% vs 92%; p = 0.141), nadir saturation (83% vs 79%; p = 0.402), or percentage time spent with saturation <90% (38% vs 52%; p = 0.308), although numeric differences are noted.

Compared with 18 subjects with an AHI ≥5/h on sleep testing, the 10 subjects using PAP at enrollment were found to be older (50 vs 63 years; p = 0.016); otherwise, there were no significant differences with respect to gender, BMI, Epworth sleepiness score, or hemodynamic data (data not shown).

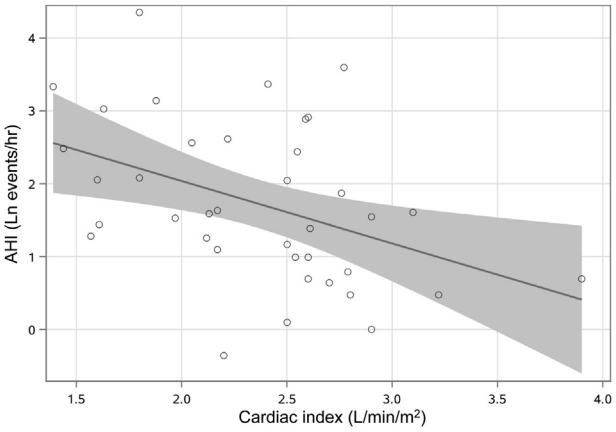

Figure 1. Cardiac index is inversely correlated with AHI (natural log transformed to satisfy normality assumption). $\beta = -0.857$, $R^2 = 0.178$; $p = 0.008$. Solid line denotes linear regression with shaded area illustrating 95% confidence interval.

All 49 subjects underwent right-sided cardiac catheterization. Cardiac index (i.e. cardiac output divided by estimated body surface area) was significantly lower in those with SDB compared with those without (Table 1). No differences were observed in cardiac output, right atrial (RA) pressure, pulmonary vascular resistance, or pulmonary artery wedge pressure.

Thirty-nine subjects underwent sleep testing, which was performed within 2 days of catheterization in 85% of subjects. Linear regression was performed to examine the effect of cardiac index on AHI, with natural log transformation applied to AHI to satisfy the normality assumption, which revealed a significant association (Figure 1). BMI and age were not found to correlate with log AHI ($p = 0.133$ and $p = 0.648$, respectively), nor was baseline saturation ($p = 0.610$). In 24 subjects in whom LFCT was scorable, there was a significant association between cardiac index and LFCT (Figure 2), using an inverse first-order model (i.e. $y = y0 + a/x$), determined a priori based on an expected hyperbolic relation. Despite association between LFCT and cardiac index and between cardiac index and log AHI, no significant correlation was found between LFCT and log AHI ($p = 0.129$). In addition, there was no significant difference in LFCT between those with AHI <5/h and those with AHI ≥5/h (Figure 2).

In subjects with a highly collapsible upper airway, SDB might be expected regardless of respiratory control stability; therefore, an a priori subgroup analysis was performed on subjects with a percentage of events that were central apneas ≥1% (i.e. ≥ the cohort median), which we believed were likely to have only a mildly collapsible airway. A linear relation between cardiac index and log AHI in this subgroup ($n = 20$) was found (Figure 3), and the mean cardiac index was lower in those with AHI ≥5/h compared with those with AHI <5/h (2.18 vs 2.55 L/min/m^2; $p = 0.036$). Additionally, there was a significant association between LFCT ($n = 14$) and log AHI ($\beta = 0.117$, $R^2 = 0.310$; $p = 0.039$). Within the subgroup, LFCT was significantly shorter in subjects with AHI <5/h compared with those with AHI ≥5/h (Figure 3).

Multiple linear regression was performed with variables known or suspected to account for severity of SDB (age, BMI, baseline saturation, RA pressure, pulmonary artery wedge pressure, and cardiac index); only BMI ($p = 0.050$) and cardiac index ($p = 0.028$) were significantly associated with log AHI. In all 49 subjects, the probability of SDB was analyzed using multiple logistic regression with covariates of age, BMI, RA pressure, pulmonary artery wedge pressure, and cardiac index. The only significant predictor of SDB in this model was cardiac index ($p = 0.046$).

Discussion

The key findings of this study are (1) SDB is highly prevalent in patients with CTEPH, and (2) cardiac index strongly predicted the presence and severity of SDB.

These results suggest that the prevalence of SDB is higher in patients with CTEPH than in the general population. Most apneas were obstructive, consistent with obstructive sleep apnea, although most events were hypopneas, which cannot reliably be distinguished on portable testing, and therefore, estimates of the prevalence of obstructive versus central sleep apnea cannot be made. Nonetheless, the major focus of this study is the potential contribution of low cardiac index to unstable breathing, which may be relevant in SDB of both obstructive and central nature.

Subjects with SDB had a significantly lower cardiac index compared with those without, and an inverse correlation between cardiac index and AHI was observed. This relation does not appear to be to be the result of confounding by body mass index, which was shown to have no correlation with cardiac index, as is consistent with previous studies.[17] As the circulatory delay is the postulated mechanism by which right ventricular impairment might lead to SDB, cardiac index was used, rather than cardiac output. Cardiac index would be expected to reflect more accurately the time it takes blood to travel to from the lungs to carotid and/or central chemoreceptors as both cardiac index and time are a function of velocity (i.e. output) and distance (i.e. body size). This assertion is further supported by the strong correlation observed between cardiac index and LFCT. The effect of cardiac index on SDB does not appear to be the result of confounding by fluid overload and rostral fluid shifts, as no difference was observed in supine RA pressure, although measures of fluid redistribution were not available.[18] In addition, the association between cardiac index and SDB remained significant in multiple regression models that accounted for other known causes of SDB. Therefore, these results suggest that low cardiac index because of right ventricular impairment contributes to SDB.

Although LFCT was well correlated with cardiac index, it did not appear to predict SDB when examined in all subjects. The most probable explanation is the imprecision in LFCT measurements and the potential influence of factors other than cardiac index, such as pulmonary function and signal noise or averaging. A trend toward correlation between LFCT and AHI was observed, so a larger sample size might have overcome the large variance in LFCT to reach significance. Nonetheless, further refining LFCT or an alternative noninvasive technique to identify those with

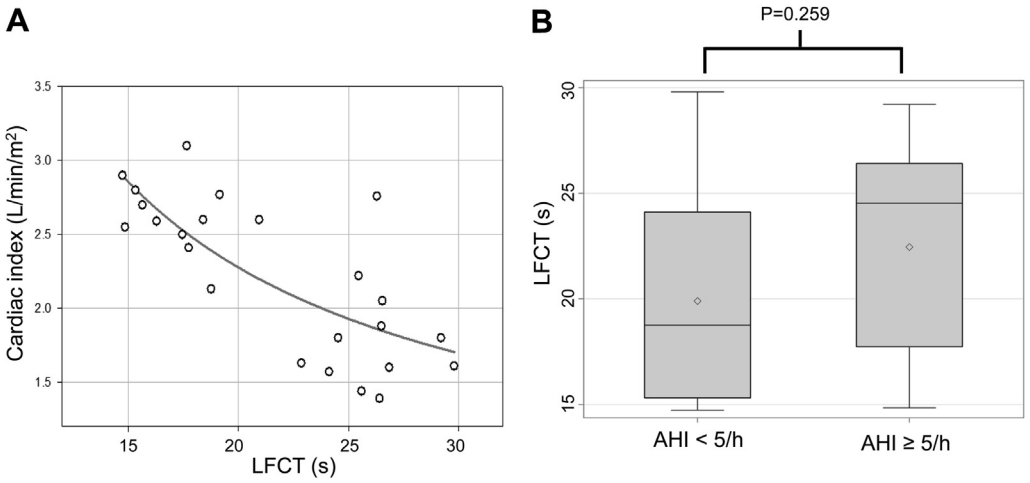

Figure 2. *(A)* Cardiac index is inversely correlated with LFCT. $R^2 = 0.543$; $p < 0.0001$. Analysis was performed using inverse first-order relation of the form $y = y0 + a/x$, with the solid curved line denoting nonlinear regression. *(B)* No significant difference was found in the LFCT between subjects with AHI <5/h and those with AHI ≥ 5/h (19.9 vs 22.5 seconds; $p = 0.259$).

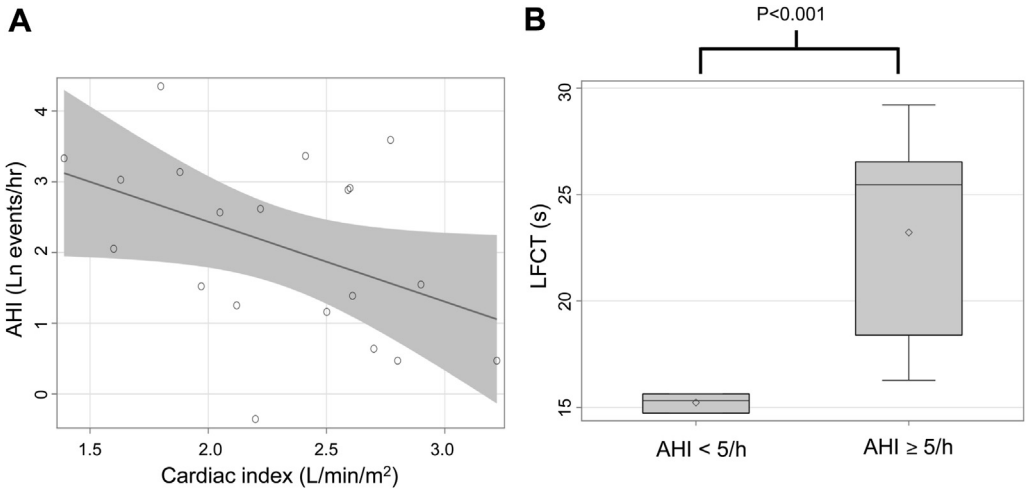

Figure 3. Effect of cardiac index and LFCT on AHI in a subgroup of 20 subjects in whom central apneas comprised >1% of events. *(A)* A nearly significant correlation between cardiac index and AHI was found in the subgroup of 20 subjects ($\beta = -1.13$, $R^2 = 0.192$; $p = 0.053$), with a numerically higher coefficient of correlation than that observed in all subjects. *(B)* Circulation time was significantly shorter in subjects with AHI <5/h compared with those with AHI ≥ 5/h (15.3 vs 23.2 seconds; $p < 0.001$).

prolonged circulatory delay as a contributing factor to SDB would likely have clinical utility.

Patients with CTEPH were observed to have a low baseline oxygen saturation, which likely contributed to the high prevalence of SDB. Patients with CTEPH have considerable ventilation/perfusion mismatching.[19] As a result, the oxyhemoglobin saturation is on the steeper part of the dissociation curve, whereby relatively small perturbations in ventilation can result in desaturation. Therefore, SDB may be "overdiagnosed" in these patients relative to those with normal oxygenation, given that desaturation is part of the criteria for respiratory events. In contrast, hypoxemia itself has been postulated to contribute to chemosensitivity and ventilatory instability.[20] There was no correlation between baseline saturation and AHI, which suggests that differences in ventilatory instability, not simply propensity to desaturate, accounts for the observed variability of SDB.

Importantly, the correlation between circulatory delay (both by cardiac index and LFCT) and SDB was more pronounced when examining the subgroup of patients with a higher proportion of central apneas. This finding supports the concept of "effect modification," in which the importance of ventilatory instability in causing SDB depends on the upper airway anatomy and function.[21] Thus, right ventricular dysfunction and resultant circulatory delay are likely most relevant to the pathogenesis of SDB in certain patients. Mechanisms by which increased circulatory delay might contribute to SDB in these patients include larger negative feedback oscillations, predisposition to upper airway collapse, and ventilatory overshoot leading to arousals.[22–24] Full polysomnography and physiological characterization

were not possible in this referral patient group, but these pilot findings appear to justify further investigation.

The consequences of SDB in CTEPH are unknown. Evidence is beginning to clarify the importance of specific manifestations of SDB, such as hypoxemia, arousals, or negative intrathoracic pressure, on outcomes such as diabetes and hypertension, which might affect this population. In addition, the presence of SDB and overall low nocturnal saturation might affect right ventricular function, although the magnitude of this effect remains controversial.[25–27]

SDB has been associated with a small but increased risk of thromboembolism and, therefore, could be a risk factor for CTEPH.[28] This study is not specifically designed to address this possibility. However, one would expect that more severe sleep apnea would have a higher likelihood of thromboembolism, whereas in this study most subjects were found to have mild SDB. In addition, although SDB might contribute to right ventricular dysfunction, other known SDB risk factors (e.g., BMI, male gender, age) were equivalent between those with and without SDB in this study, arguing against this direction of causality.

As a pilot study, there are methodologic limitations. Portable sleep testing is potentially less accurate than polysomnography, although generally biases toward underestimation of AHI. Referral bias in this cohort could reduce generalizability of the findings but because surgical evaluation is broadly indicated, the effect is likely small. Intensive physiological study of SDB was not possible here but would be needed to more definitively control for all confounding factors. Follow-up data showing a reduction in SDB after pulmonary thromboendarterectomy surgery with associated right ventricular function improvement would further validate the findings from this study. Furthermore, understanding whether improving cardiac index and decreasing circulatory delay results in improvement in SDB would have broad clinical relevance.

Acknowledgment: The authors thank Bradley A. Edwards, PhD, and Scott A. Sands, PhD, for discussions regarding ventilatory control theory.

Disclosures

The authors have no conflicts of interest to disclose.

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