Circulation Time Measurement from Sleep Studies in Patients with Obstructive Sleep Apnea

Yoonhoon Kwon, M.D.^{1,2}; Talha Khan, M.D.³; Marc Pritzker, M.D.¹; Conrad Iber, M.D.²

¹Hennepin County Medical Center, Minneapolis, MN; ²University of Minnesota, Minneapolis, MN;

³Medical College of Wisconsin, Milwaukee, WI

Introduction: Lung to finger circulation time (LFCT) can be estimated from polysomnography (PSG) in the presence of an apneic event by using oxygen as an indicator and a finger as the site of detection. The purpose of this study was to refine the methodology of LFCT measurement and to compare LFCT in patients with obstructive sleep apnea (OSA) with and without heart failure (HF).

Methods: In a retrospective manner, 10 LFCT measurements per patient were made from the PSG in 171 consecutive patients with a diagnosis of OSA who were divided into two groups: (a) those with a clinical history of underlying HF (N = 42) and (b) those without HF (N = 129). Mean values were compared between the two groups. We also examined associations of LFCT with various factors in each group and the combined group separately using multiple regression analysis.

Results: Gender and age were significantly associated with

LFCT in patients with OSA alone. Use of β -blockers was associated with LFCT in the group with OSA with HF. Among the entire cohort, HF, β -blocker, gender, and age were found to be significantly associated with LFCT. The presence of HF was the strongest predictor of a prolonged LFCT (adjusted mean LFCT: OSA only = 18.5 [95% CI: 17.2-19.7 sec] vs. OSA with HF = 26.1 [95% CI: 24.3-28.0 sec], $p < 0.0001$).

Conclusion: LFCT can be reliably measured and is prolonged in patients with OSA and underlying HF. LFCT based on PSG may be a useful marker for detection of coexisting HF in patients with OSA.

Keywords: circulation time, heart failure, obstructive sleep apnea

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Although measurement of lung to periphery circulation time from PSG has been described, its use has been limited due to uncertainty of methodology and lack of known clinical implication. Standardizing methodology and defining the factors affecting circulation time may be important in defining the utility of this measure in clinical and research settings.

Study Impact: LFCT can be reliably measured from PSG within subjects and was prolonged in patients with a clinical diagnosis of HF. Prospective studies are needed to define the role of prolonged LFCT identified during the PSG in determining likelihood of coexisting HF.

The diagnosis of heart failure (HF) confers a high likelihood of a concomitant sleep related breathing disorder (SRBD) with Cheyne-Stokes respiration-central sleep apnea (CSR-CSA) or obstructive sleep apnea (OSA) occurring in 20% to 60% of HF patients.^{1,2} The severity of HF influences the likelihood of a SRBD and the proportion of obstructive vs. central respiratory events in a given patient.^{3,4} Furthermore, the presence of SRBD is associated with adverse outcomes in HF.⁵ Thus, identification of polysomnography (PSG)-derived markers of HF during sleep studies may have important implications for prognosis and management. Although CSR-CSA is a recognized physiologic pattern unique to HF,⁶ additional physiologic patterns acquired during sleep studies may prove useful in the discovery of unsuspected HF in patients with suspected OSA.

Circulation time (Ct) is defined as the time it takes for a given indicator to reach the place of detection, and its measurement is based on the "indication-dilution" method. While Ct has been frequently used in the past to approximate cardiac output,⁷ emergence of advanced technologies that provide more accurate evaluation have largely replaced this metric. Resurgence of interest in Ct has been driven by more precise measures using modern imaging tools such as radionuclide imaging, computerized tomography, and magnetic resonance imaging techniques.⁸⁻¹⁰ One simple method of obtaining Ct is by using oxygen (O_2) as an indicator, the lung as an injection site, and the periphery as a detection site. Kasravi et al.¹¹ demonstrated lung to finger Ct (LFCT) of O_2 , which was measured from the

onset of 100% O_2 administration to the peak in O_2 saturation and showed its inverse relationship against invasively measured cardiac output. In similar manner, lung to periphery time can be obtained from PSG in the presence of clearly defined apneic or hypopneic episodes accompanying O_2 desaturation. If transit time through conductive airway can be ignored, lung to periphery Ct can be defined by the time interval from the starting point of a recovery breath (hyperpnea) that follows the apnea to the ensuing nadir point of O_2 desaturation as measured at a peripheral site (**Figure 1**). This time interval represents the approximate O_2 transport time from lung to periphery and forms the basis for PSG-based Ct measurement in CSR.¹² The possibility of using Ct as a method to identify evidence for HF in patients with OSA has been explored in a previous study by Ryan et al.,¹³ in which characteristics of respiratory pattern such

Figure 1—Illustration of lung to finger circulation time (LFCT) measurement from PSG.

Measurement starting point is at the point of hyperpnea following apnea or hypopnea (Hyp). Ending point of the measurement is at the nadir of oxygen (O_2) desaturation. NASAL PRESS, nasal pressure (NP) channel. ORAL THERMAL, thermocouple flow (TF) channel. THOR & ABD, thoracic and abdominal respiratory inductance plethysmograph (RIP) channel. $SpO_2\%$, pulse oximetric O_2 saturation.

as hyperpnea duration, total apnea-hyperpnea cycle length, and Ct were examined. In that study, lung to ear Ct (LECT) was significantly prolonged in OSA patients with coexisting HF as compared to those with OSA only.

Indeed Ct can be easily assessed in patients with OSA by clinicians reading PSG. However, its clinical application has been limited by lack of a consistent methodology and limited reference data comparing patient groups. In addition, unlike LECT, which has been previously examined in small number of subjects,¹³ PSG-based LFCT measures have not been formally investigated despite the fact that the finger probe has replaced the ear probe as the standard measure in clinical sleep laboratories. In this pilot study, we sought to establish consistent methods and reference data for PSG-based LFCT by defining a method with reproducible measures and causes for measurement variability. We hypothesized that LFCT could be reliably measured from the PSG and that it would be prolonged in patients with OSA and underlying HF.

MATERIALS AND METHODS

Study Subjects

We reviewed PSGs between December 2005 and February 2011 performed at the Minnesota Regional Sleep Disorder Center sleep laboratory. Patients were divided into 2 main groups: (1) patients with OSA but without HF (OSA only), and (2) patients with OSA and a coexisting clinical diagnosis of chronic HF (OSA with HF). In both groups, subjects were excluded if (1) they were currently receiving therapy for a SRBD, (2) there was a history of chronic pulmonary disease requiring O_2 therapy, or (3) there was recent cardiothoracic surgery.

OSA Only Group

Consecutive subjects with a PSG finding of OSA as defined by AHI of $> 5/h$ were identified from December 2010 through February 2011. Subjects were excluded from this group if there was any clinical evidence of HF including lower extremity edema, dyspnea on exertion, exercise intolerance, orthopnea, crackles in the lung, elevated jugular venous distension, or ventricular or atrial gallops on auscultation.

OSA with HF Group

Consecutive subjects with a PSG finding of OSA as defined by an AHI $\geq 5/h$ and a documented history of HF were identified from December 2005 and February 2011. All of the subjects in this group had an echocardiographic report supportive of at least one of the following interpretations within a year from the time of sleep study: left ventricular systolic (ejection fraction [EF] $< 40\%$) and/or diastolic dysfunction or right ventricular dysfunction.

This study was approved by the Institutional Review Board at Hennepin County Medical Center (Project number 11-1930X).

Polysomnographic Measurements

All overnight sleep studies were performed with standard PSG techniques.¹⁴ The same sensor devices and software (Compumedics, Abbotsford, Victoria, Australia) were used in all patients. For identification of respiratory timing during circulation time estimates, both nasal pressure (NP; Salter Labs-Binaps, CA, USA) and thermocouple flow (TF; Salter Labs-Thermisense, CA, USA) channels were employed. Respiratory inductance plethysmography (RIP; Respirationics, Andover, MA, USA) was used to measure thoracoabdominal movements. Pulse oximeter oxygen saturation (SpO_2) was measured continuously (averaging time 3 sec, Nonin, Plymouth, MN, USA) from the fingertip. Sleep stages and respiratory events were scored according to standardized criteria.¹⁴ Obstructive apnea was scored when the TF amplitude decreased by $\geq 90\%$ of baseline for ≥ 10 sec. Obstructive hypopnea was scored when the NP amplitude decreased by $\geq 30\%$ of baseline for ≥ 10 sec accompanied by O_2 desaturation $\geq 4\%$ with persistent respiratory efforts on RIP. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. The severity of OSA was classified as mild ($5 \leq AHI < 15/h$), moderate ($15 \leq AHI < 30/h$), or severe OSA ($AHI \geq 30/h$), respectively. LFCT was obtained during the diagnostic stage of the sleep study by measuring the time interval from the starting point of the recovery hyperpnea to the nadir of O_2 desaturation following the respiratory event (Figure 1). These events were typically measured during hypopneas, given the preponderance of hypopneas relative to apneas. Because of the limited REM sleep (stage R) during the baseline component

of split-night sleep studies and the more variable breathing pattern during this stage, measurements of LFCT were made only during the most abundant stage, N2 sleep.

METHODS

For the purpose of refining our methodology, we conducted a pilot study in a small number of PSG cases to identify a method that would provide an easily applicable measurement with the least amount of variability. We focused on choosing a sensor that reliably identifies the starting point of recovery hyperpnea, which we deemed to be the most crucial step in the LFCT measurement. Specifically, we compared airflow measurements obtained from the NP and TF channels. PSGs of 22 cases with a diagnosis of OSA were randomly selected from 4 different groups (mild [$N = 5$], moderate [$N = 5$], severe OSA [$N = 9$], and OSA with HF [$N = 3$]). In each case, an average of 10 consecutive measurements of LFCT, together with the duration of the obstructive event, was made from stage N2 sleep using both the NP and TF channels. Measurements were generally taken during the first half of the sleep study (during the diagnostic portion), as the majority of the patients were on treatment with positive pressure during the latter half of the sleep study. The mean and coefficient of variation of the LFCT measurements were calculated for each patient. Pooled averages of the means and coefficients of variation were then derived for all the patients in order to compare the coefficient of variation between the 2 methodologies (NP vs. TF).

Next, the method determined to have higher reliability of repeated measures (NP vs. TF) was then employed for further analysis of the entire cohort including those with OSA only ($N = 129$) and those with OSA with HF ($N = 42$). The results from aforementioned pilot study ($N = 22$) were incorporated into this data. An average of 10 consecutive LFCT measurements were made as described above. For moderate to severe OSA cases, the 10 measurements were obtained within a period of time on average over 1 h, whereas for mild OSA cases measurements were made over 3-4 hours. Only respiratory events with a clear onset of the first recovery breath were used for measurement. LFCT was expressed as seconds (sec).

Statistical Analysis

Values were expressed as mean $\pm$ SD. Comparison of variables between the 2 patient groups (OSA only vs. OSA with HF) were made using a 2-tailed unpaired *t*-test for continuous variables and a χ^2 test or Fisher exact test as appropriate for categorical variables. To examine independent association between explanatory variables and LFCT, multiple regressions were performed in each group. Prespecified variables included gender, therapy with β -blocker, age, weight, height, and AHI. Analysis of both groups combined (171 patients) was then performed using variables found to be significantly associated in either group while designating HF as a fixed covariate. Variables leading to multicollinearity (variance inflation factor > 0.25) were then removed from the model. Adjusted means for variables of interest were derived using a general linear model. An interaction term was not included in the initial model since the main aim of the regression analysis in this

Figure 2—Bland-Altman plot depicting agreement between LFCT measured by nasal pressure (NP) and thermocouple flow (TF) channel.

Mean difference (Bias) was 0.65 (sec).

group was to explore variables with significant association in the absence of *a priori* expectation of any particular interaction but was later applied as part of the post hoc analysis. Specifically, interactions between HF and age, β -blocker therapy, and gender were examined. A value of $p < 0.05$ was considered statistically significant in all cases including the interaction test. All statistical analyses were performed using SAS software v. 9.2 (SAS Institute Inc. Cary, NC, USA).

RESULTS

Comparison of reproducibility of LFCT measures derived from the 2 different air flow channels (NP and TF) ($N = 22$) LFCT measurements obtained using the 2 airflow channels were highly correlated ($r = 0.97$, $p < 0.0001$), but measurements using NP were more reproducible. Although the LFCT derived from the 2 methods showed reasonable agreement, there was a consistent tendency for slightly lower values using TF as compared to NP (**Figure 2**) that may be attributable to differences in sensor response characteristics. Overall, within subject variability of LFCT was substantially lower when measurements were obtained with NP (average coefficient of variation: 0.04 vs. 0.19, $p < 0.001$), and LFCT estimated by NP was slightly longer than TF (18.2 ± 0.8 vs. 17.5 ± 3.1 sec, $p = 0.03$). No significant correlation was found between the LFCT and the duration of obstructive events. Based on these results, the NP channel was used for subsequent determinations of LFCT for the entire cohort of patients.

OSA Only Group ($N = 129$)

Baseline characteristics and the mean LFCT (95% CI: 16.6-18.1) are shown in **Table 1**. The OSA only group tended to be middle-aged (64% of the cohort were 40-60 years old), moderate to severely obese (67% of the cohort had BMI ≥ 30), predominantly male (71%), and having moderate to severe OSA (85% of the cohort had AHI ≥ 15 /h). No difference in LFCT was found among groups stratified into 3 levels of OSA severity (**Table 2**). The distribution of LFCT was slightly skewed to the right. There was a modest but statistically significant correlation between LFCT and height ($r = 0.3$;

$p < 0.001$), but not with other continuous variables including AHI and BMI (**Figure S1**, supplemental material). Unadjusted LFCT was significantly longer in males than females (18.3 ± 4.6 vs. 14.9 ± 3.0 sec, $p < 0.001$). This difference remained significant even after adjusting for other variables including height (mean difference: 3.3 sec, $p = 0.005$). The adjusted mean LFCT for males and females are shown in **Figure 3**. After adjusting for other variables, height failed to show a significant association with LFCT while age emerged as a significant factor (**Table 3**).

OSA with HF Group (N = 42)

Based on the echocardiographic findings, approximately half the patients in this group were characterized as having systolic HF (N = 22, Mean EF = $33\% \pm 8.6\%$), while the rest of the patients had diastolic dysfunction (N = 13) or right ventricular failure (N = 7).

LFCT was considerably prolonged and widely distributed (Mean: 28 sec, 95% CI: 25-30.9 sec) in HF patients. Age was the only continuous variable that was significantly correlated with LFCT ($r = 0.37$, $p = 0.02$). Unlike the OSA only group, there was no significant difference in LFCT between males and females (28 ± 10.4 vs. 27.9 ± 7.4 sec, $p = 0.99$). Use of β -blockers was associated with longer LFCT (31.8 ± 9.4 vs. 20.9 ± 3.7 sec, $p < 0.001$) and was the only factor independently

associated with LFCT. The adjusted mean LFCT for patients with β -blocker use vs. no β -blocker use were 31.7 (95% CI: 28.5-34.8) and 22.2 (95% CI: 17.9-26.5) sec, respectively.

Comparison between OSA only vs. OSA with HF (N = 171)

Mean LFCT of the OSA group with HF was significantly prolonged (**Figure 4**) compared to the group without HF (28 ± 9.4 vs. 17 ± 4.5 sec, $p < 0.0001$). In multivariate analysis, the presence of HF, β -blocker use, and male gender were associated with prolonged LFCT (**Table 4**). LFCT tended to increase relative to age but this did not reach statistical significance. The adjusted mean LFCT for OSA only vs. OSA with HF were 18.5 (95% CI: 17.2-19.7) and 26.1 (95% CI: 24.3-28.0) sec, respectively ($p < 0.0001$). A significant interaction was found between HF and β -blocker use. Use of β -blockers was associated with a prolonged LFCT only in OSA with HF group, but not in OSA only group.

DISCUSSION

This report documents a method for reproducible determination of LFCT in patients with OSA and identifies variables that influence the measurement. The findings confirm that HF results in prolongation of the LFCT in this group of patients.

Table 1—Characteristics of all patients based on HF status

	OSA only (N = 129)	OSA with HF (N = 42)	p value
AHI (events/h)	35 ± 26 [7–130]	49 ± 27 [10–103]	0.002
Age (years)	48 ± 12	60 ± 11	< 0.0001
Female N (%)	37 (29)	13 (31)	0.78
Hypertension N (%)	76 (59)	38 (90)	0.0002
Diabetes N (%)	34 (26)	20 (47)	0.017
Use of β -blocker N (%)	18 (14)	27 (64)	< 0.0001
BMI (kg/m ²)	38 ± 10	37 ± 9	0.77
Height (inches)	68 ± 4	68 ± 8	0.64
Weight (lbs)	249 ± 70	254 ± 64	0.65
LFCT (sec)	17.3 ± 4.5 [9.7–33.3]	28 ± 9.4 [16.5–58.7]	< 0.0001

AHI, apnea hypopnea index; BMI, body mass index; HF, heart failure; LFCT, lung to finger circulation time; OSA, obstructive sleep apnea. Data presented as mean $\pm$ standard deviation [range].

Figure 3—Mean LFCT based on the gender in OSA only group.

Bar graph with 95% CI. * $p < 0.05$.

Table 2—Characteristics of patients in OSA only group as stratified by OSA severity

	Mild (N = 20)	Moderate (N = 60)	Severe (N = 49)	p value
AHI (events/h)	13 ± 3 [6.8–14.5]	24 ± 4 [15–29.9]	53 ± 27 [30–130]	NA
Age (years)	45 ± 11	50 ± 13	41 ± 11	0.07
BMI (kg/m ²)	37 ± 9	36 ± 10	40 ± 11	0.07
Height (inches)	$68 \pm 5^{a,b}$	67 ± 4^a	69 ± 3^b	0.03
Weight (lbs)	238 ± 62^a	231 ± 68^a	274 ± 69^b	0.005
Female N (%)	9 (45)	22 (37)	6 (12)	0.004
LFCT (sec)	16.4 ± 3.7 [11.9–25.3]	17.2 ± 4.5 [9.7–32.1]	17.9 ± 4.7 [10.4–33.3]	0.43

AHI, apnea hypopnea index; BMI, body mass index; LFCT, lung to finger circulation time; OSA, obstructive sleep apnea; NA, not applicable. Data presented as mean $\pm$ standard deviation [range]. Across rows, alphabet characters not shared imply statistically significant difference.

Circulation Time Methodology

The first aim of this study was to develop a method of PSG-based Ct measurements in patients with OSA. Our results demonstrate that using an NP based air flow channel, LFCT measurements during N2 sleep is highly reproducible when performed using modest sampling of measures and a consistent methodology. To our knowledge, this represents the first report that specifically addresses a standard methodology for measuring LFCT from PSG and explores factors that influence PSG-derived CT in patients with OSA. Although the concept of measuring lung to periphery Ct from PSG has been described in the context of CSR-CSA, the examination on OSA is uncommon.^{12,13} In addition, previous studies used ear rather than finger as the peripheral site of indicator (O_2) detection in order to estimate the lung to chemoreceptor Ct. In practice, however, the fingertip is the most commonly used site for pulse oximetry. Because of this, we felt the need to evaluate the feasibility of LFCT measurement and to construct normative LFCT data that could be used for future reference. Obstructive respiratory events that result in oxygen desaturation provide the opportunity for Ct measurements during PSG. However, no standardized method has been reported to allow meaningful comparison of LFCT across patients. Moreover, the reproducibility of such measurements has been unclear. We thus focused our efforts on comparing the two conventionally used air flow channels, TF and NP, in terms of their visual quality in defining the onset of recovery hyperpnea and their reproducibility in measuring LFCT within a PSG. From a measurement perspective, while nadir of oxygen desaturation (the ending point of Ct determination) is generally unequivocal, determining onset of recovery hyperpnea (the starting point of Ct) using non-quantitative flow measures such as TF would be expected to be less reliable during hypopneas, which constitute the majority of events in OSA. Because confirmation of augmentation of airflow is required for the determination of hyperpnea, a semiquantitative measure such as NP would be expected to be less variable.¹⁵ Indeed, we found the NP channel to yield lower variability as measured by coefficient of variation. This may be explained by the well-recognized nonlinearity in TF measures. Using the NP sensor, the distribution of 10 consecutive measures of LFCT was acceptably narrow taking into account physiological variability. The slightly shorter LFCT measurements with TF may reflect differences in response time of this device.

Our effort to extend LFCT measurements into stage R sleep was challenging. First, many patients did not exhibit stage R sleep during the diagnostic portion of the split-night study, thus reducing the number of repeated LFCT measurements available for analysis. Second, the onset of hyperpnea was not always clear. In stage R sleep, inherent respiratory variability and periods of respiratory muscle inhibition increase uncertainty in defining the onset of hyperpnea due to relief of obstruction.^{16,17} Consequently, for the purpose of this study, we decided not to make a direct comparison of LFCT obtained from stage R sleep to that from stage N sleep. However, recognizing the much higher frequency of obstructive events and thus more opportunities for LFCT measurements in stage R sleep, characterization of the LFCT measurements comparing stage N vs. stage R should be considered for future studies.

Table 3—Variables associated with LFCT in patients with OSA only

Variable	Regression coefficients	p value
Male (vs. Female)	3.3	< 0.005
β -blocker use (vs. no use)	0.6	0.62
Age (/10 years)	0.8	0.03
Weight (/lb)	0.01	0.13
Height (/inch)	0.14	0.28
AHI (per 1 event/h)	-0.02	0.30

AHI, apnea hypopnea index; LFCT, lung to finger circulation time; OSA, obstructive sleep apnea.

Table 4—Variables associated with LFCT in all patients

Variable	Regression coefficients	p value
HF (vs. no HF)	7.7	< 0.001
β -blocker use (vs. no use)	4.4	< 0.001
Male (vs. Female)	3.2	< 0.001
Age (/10 years)	0.7	0.06

AHI, apnea hypopnea index; HF, heart failure; LFCT, lung to finger circulation time.

Figure 4—Box-Whisker plot of LFCT comparing OSA only group vs. OSA with HF group (unadjusted comparison).

Factors Affecting Circulation Time in Patients with OSA

The data from our cohort allows us to make a plausible inference as to the LFCT in patients with OSA at a population level. Distribution of the LFCT in our patients with OSA alone was slightly skewed to the right. Although this may represent the inherent distribution pattern of the LFCT in OSA, it is possible that a larger sample size might approximate a more normal distribution. In addition, there are two potential explanations for this finding: (1) obstructive events may acutely alter cardiac output, and (2) the exclusion of HF was imprecise. Given the known effects of obstructive apnea events on cardiac output,¹⁸ we suspect the skewing reflects the impact of OSA on Ct in some patients. Moreover, the retrospective nature of the study raises the concern that mild HF may have been undetected in the OSA only group.

We found gender and age to be significantly associated with a prolonged LFCT in patients with OSA alone. Although gender differences in height (and therefore arm length) is one potential cause for the longer LFCT in males, a longer mean LFCT was observed in men even after accounting for height. In fact, while a longer Ct is expected with a longer course of circulation (as demonstrated by the difference between LECT and LFCT), we did not find any anthropometric factor such as height or weight to be significantly related to LFCT in a multivariate analysis. Although previous data reported similar proportions between arm length and height,¹⁹ direct measures of arm length would be necessary to absolutely exclude this mechanism as a cause for the observed gender difference. A small but statistically significant correlation between LFCT and age was observed (0.7 sec longer for every 10 years of age). It is possible that the reported reduction in cardiac output with age may be responsible for this finding.²⁰

The severity of OSA as defined by AHI was not significantly correlated with LFCT. From a physiological perspective, this is not surprising as there is no plausible reason to link number of obstructive events or AHI with LFCT. Although not measured in our study, one can speculate that the degree of immediate hemodynamic compromise during obstructed breathing might have an influence on the Ct. Thus, exaggerated negative intrathoracic pressure induced by obstructive inspiration and slowing of the heart rate can produce periodic reductions in cardiac output that could prolong the measured LFCT during obstructive events.^{18,21,22}

Circulation Time Measures Comparing Groups with and without HF

The major finding of our study is the prolongation of LFCT in the HF as compared to OSA only group. As previously shown by Ryan et al.,¹³ the delay in Ct is manifested even in patients with HF whose PSG finding primarily features OSA but not the classic CSR-CSA. This finding suggests that the lung to periphery Ct measured from obstructive events in the setting of OSA is a valid estimate of circulation delay. It should be noted that the mean LFCT (28 ± 9.5 sec) in the “OSA with HF” group in our study should not be directly compared to the LECT (24.2 ± 2 sec) reported by Hall et al., as the latter represents Ct measured using ear as a detection site from CSR-CSA.¹²

Finally, along with HF, β -blocker use was independently associated with a prolonged LFCT. Interestingly, a significant interaction between HF and β -blocker was present with the effect of β -blocker on Ct present only in patients with HF. An acute effect of β -blocker use on Ct has been demonstrated in a placebo-controlled experiment in which LECT was shown to increase following atenolol both at rest and during exercise.²³ The effect of long-term β -blocker therapy on Ct is complex because of the variable chronotropic and inotropic responses in this population.

In general, despite improvement of several parameters of cardiac function such as stroke volume, cardiac output per se has been shown to decrease with the long term use of β -blocker therapy primarily driven by a reduction in heart rate.²⁴

While there are a variety of methods to measure Ct, most of them, including LFCT, are based on the indicator dilution technique. It is important to recognize that the measured

Ct represents the time it takes an injected indicator to reach a detectable concentration at the place of detection rather than actual time it takes for an indicator to arrive.²⁵ Because of this, measured Ct can vary depending on the method used. Importantly, Ct obtained by our method may have been further prolonged because of the two aforementioned mechanisms: (1) transient decreases in cardiac output as a result of the hemodynamic consequences of inspiration against an obstructed airway,²¹ and (2) the longer pulmonary transit time related to breath holding.²² It is equally important to recognize that the acute hemodynamic effects of apnea can differ significantly between patients with and without normal cardiac function.²⁶

Our study has several important limitations. First, the retrospective nature of the study may have resulted in information bias. Investigators involved in the LFCT measurement were not blinded as to the diagnosis of HF. We would argue that the LFCT measurement is an objective linear task that is not subject to interpretive bias. Ct as measured by our method can be influenced by the inherent instrumental delay of the pulse oximetry. This effect would be similar in all patients and therefore would be unlikely to influence the differences between the two groups. In addition, although the overall mean variation of Ct within a subject was low, moderately wide variations were occasionally noted, thus rendering caution to simply basing Ct on one random measurement. Next, although this study has merit in exploring LFCT in a field setting using a clinical diagnosis of HF, characterization of the severity HF at the time of the LFCT measures may have been imprecise given the retrospective nature of the study. We did not perform simultaneous assessment of cardiac function utilizing tools such as right heart catheterization or other noninvasive cardiac imaging techniques coinciding with the time of sleep study, and thus we were not able to quantify the relation of LFCT to variables known to influence Ct such as cardiac output, filling pressures of the right and left heart (as surrogates to volume status), and cardiac chamber size.²⁵ We recognize that such information obtained prospectively will be crucial to further validate our results in defining the differences between OSA patients with and without HF. The clinical utility of LFCT certainly deserves further exploration with careful attention to methodologies employed such as those examined in this study. In clinical sleep laboratories considering the measurement of LFCT, it is also important to note that LFCT may be affected by the averaging time or smoothing techniques employed by a particular pulse oximeter. Finally, the wide distribution of LFCT observed in a heterogeneous group of patients with varying HF severities makes it difficult to propose LFCT as an accurate screening tool to exclude HF at this time. In this context, a prolonged LFCT can be used to alert providers to possible underlying HF but should not be used alone as discriminatory finding when considering HF in patients with OSA.

Despite these limitations, we believe that LFCT can serve as a useful tool to monitor the cardiac condition of a patient on the premise of acceptable night to night variability. Future prospective studies of LFCT would address unresolved issues. These investigations should examine the use of multiple measures from sleep studies including LFCT, the length of apnea cycles, and duration of hyperpnea to improve the discriminatory power of these measures in comparing OSA alone vs. OSA with HF.^{12,13}

In conclusion, our findings demonstrate that LFCT can be easily and reliably measured in patients with OSA from PSG. The most significant factor associated with a delay in LFCT was underlying HF. This effect became more marked in the presence of β -blocker use. The present findings provide the basis for additional prospective studies to explore the clinical utility of LFCT in patients with OSA.

ABBREVIATIONS

Ct, circulation time
HF, heart failure
LFCT, lung to finger circulation time
NP, nasal pressure
OSA, obstructive sleep apnea
PSG, polysomnography
TF, thermocouple flow

REFERENCES

1. Wang H, Parker JD, Newton GE, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol* 2007;49:1625-31.
2. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. *Eur J Heart Fail* 2007;9:251-7.
3. Tkacova R, Hall MJ, Liu PP, Fitzgerald FS, Bradley TD. Left ventricular volume in patients with heart failure and Cheyne-Stokes respiration during sleep. *Am J Respir Crit Care Med* 1997;156:1549-55.
4. Tkacova R, Niroumand M, Lorenzi-Filho G, Bradley TD. Overnight shift from obstructive to central apneas in patients with heart failure: role of PCO₂ and circulatory delay. *Circulation* 2001;103:238-43.
5. Yumino D, Wang H, Floras JS, et al. Relationship between sleep apnoea and mortality in patients with ischaemic heart failure. *Heart* 2009;95:819-24.
6. Pryor WW. Cheyne-Stokes respiration in patients with cardiac enlargement and prolonged circulation time. *Circulation* 1951;4:233-8.
7. Blumgart H. The velocity of blood flow in health and disease. The velocity of blood flow in man and its relation to other measurements of the circulation. *Medicine* 1931;10.
8. Jones RH, Sabiston DC Jr., Bates BB, Morris JJ, Anderson PA, Goodrich JK. Quantitative radionuclide angiography for determination of chamber to chamber cardiac transit times. *Am J Cardiol* 1972;30:855-64.
9. Muller HM, Tripolt MB, Rehak PH, Groell R, Rienmuller R, Tscheliessnigg KH. Noninvasive measurement of pulmonary vascular resistances by assessment of cardiac output and pulmonary transit time. *Invest Radiol* 2000;35:727-31.
10. Shors SM, Cotts WG, Pavlovic-Surjancev B, Francois CJ, Gheorghide M, Finn JP. Heart failure: evaluation of cardiopulmonary transit times with time-resolved MR angiography. *Radiology* 2003;229:743-8.
11. Kasravi B, Boehmer JP, Leuenberger UA. A noninvasive method for estimating cardiac output using lung to finger circulation time of oxygen. *Am J Cardiol* 1998;82:915-7.
12. Hall MJ, Xie A, Rutherford R, Ando S, Floras JS, Bradley TD. Cycle length of periodic breathing in patients with and without heart failure. *Am J Respir Crit Care Med* 1996;154:376-81.
13. Ryan CM, Bradley TD. Periodicity of obstructive sleep apnea in patients with and without heart failure. *Chest* 2005;127:536-42.

14. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.
15. Norman RG, Ahmed MM, Walsleben JA, Rapoport DM. Detection of respiratory events during NPSG: nasal cannula/pressure sensor versus thermistor. *Sleep* 1997;20:1175-84.
16. Schafer T, Schlafke ME. Respiratory changes associated with rapid eye movements in normo- and hypercapnia during sleep. *J Appl Physiol* (1985) 1998;85:2213-9.
17. Gould GA, Gugger M, Molloy J, Tsara V, Shapiro CM, Douglas NJ. Breathing pattern and eye movement density during REM sleep in humans. *Am Rev Respir Dis* 1988;138:874-7.
18. Guilleminault C, Motta J, Mihm F, Melvin K. Obstructive sleep apnea and cardiac index. *Chest* 1986;89:331-4.
19. Fredriks AM, van Buuren S, van Heel WJ, Dijkman-Neerincx RH, Verloove-Vanhorick SP, Wit JM. Nationwide age references for sitting height, leg length, and sitting height/height ratio, and their diagnostic value for disproportionate growth disorders. *Arch Dis Child* 2005;90:807-12.
20. Brandfonbrener M, Landowne M, Shock NW. Changes in cardiac output with age. *Circulation* 1955;12:557-66.
21. Tolle FA, Judy WV, Yu PL, Markand ON. Reduced stroke volume related to pleural pressure in obstructive sleep apnea. *J Appl Physiol Respir Environ Exerc Physiol* 1983;55:1718-24.
22. Krinsky GA, Kaminer E, Lee VS, Rofsky NM, Weinreb JC. The effects of apnea on timing examinations for optimization of gadolinium-enhanced MRA of the thoracic aorta and arch vessels. *J Comput Assist Tomogr* 1998;22:677-81.
23. Wolff CB, Checkley SK, Bhagerrutti G et al. Circulation time in man from lung to periphery as an indirect index of cardiac output. *Adv Exp Med Biol* 2005;566:311-6.
24. Nodari S, Metra M, Dei Cas L. Beta-blocker treatment of patients with diastolic heart failure and arterial hypertension. A prospective, randomized, comparison of the long-term effects of atenolol vs. nebivolol. *Eur J Heart Fail* 2003;5:621-7.
25. Pearce ML, Lewis AE, Kaplan MR. The factors influencing the circulation time. *Circulation* 1952;5:583-8.
26. Bradley TD, Hall MJ, Ando S, Floras JS. Hemodynamic effects of simulated obstructive apneas in humans with and without heart failure. *Chest* 2001;119:1827-35.

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Address correspondence to: Younghoon Kwon, M.D., Cardiovascular Division, University of Minnesota, Mayo Mail Code 508, 420 Delaware St. SE, Minneapolis, MN 55455; Tel: (612) 625-7924; Fax: (612) 626-4411; E-mail: kwonx208@umn.edu

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SUPPLEMENTAL MATERIAL

Figure S1—Scatter plot with fitted regression line.

LFCT (lung to finger circulation time) vs. **(A)** apnea hypopnea index (AHI) **(B)** body mass index (BMI). r , correlation coefficient.