Published in final edited form as:

Sleep Med. 2020 November ; 75: 8–11. doi:10.1016/j.sleep.2020.05.033.

Lung to Finger Circulation Time in Sleep Study and Coronary Artery Calcification: The Multi-Ethnic Study of Atherosclerosis [Brief Communication]

Younghoon Kwon¹, Sara Mariani², Michelle Reid², David Jacobs Jr³, Joao Lima⁴, Vishesh Kapur¹, Naresh Punjabi⁴, Susan Redline²

¹University of Washington

²Harvard Medical School, Brigham and Women's Hospital

³University of Minnesota

⁴Johns Hopkins School of Medicine

Abstract

Lung to finger circulation time (LFCT) measured from sleep studies may represent a novel physiologic marker for cardiovascular risk in patients with sleep disordered breathing (SDB). We hypothesized that sleep study-derived LFCT would improve risk classification of markers of subclinical cardiovascular disease. We included participants in the Multi-Ethnic Study of Atherosclerosis (MESA) Sleep cohort with moderate-severe SDB (apnea hypopnea index [AHI] 15/hr) (N=598). Those with average LFCT above the median (19.4 sec) (vs. shorter LFCT) tended to be older, more obese and male. In multivariable analysis, no significant associations were found between average LFCT and subclinical cardiovascular markers including coronary artery calcium, carotid intima-media thickness or left ventricular hypertrophy. However, there was modest improvement in risk classification of coronary artery calcification as compared with AHI alone when average LFCT was added to AHI (C statistics 0.53 vs. 0.62, $p=0.0066$). In conclusion, LFCT may be a useful addition to conventional SDB metrics to improve cardiovascular risk assessment.

CRedit author statement

Younghoon Kwon: conceptualization, methodology, investigation and writing original draft

Sara Mariani: methodology, data curation, investigation

Michelle Reid: formal analysis, visualization, writing-review and editing

David Jacobs Jr: methodology, writing-review and editing

Joao Lima: investigation, writing-review and editing

Vishesh Kapur: writing-review and editing

Naresh Punjabi: investigation, writing-reviewing and editing

Susana Redline: conceptualization, writing-reviewing and editing and funding acquisition

Declarations of interest: none.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

atherosclerosis; cardiovascular; coronary artery calcium; circulation; polysomnography; sleep apnea

Sleep disordered breathing (SDB) is a common condition that is increasingly recognized as an important risk factor for cardiovascular (CV) risk and morbidities including hypertension, stroke, coronary heart disease (CHD) and heart failure [1–3]. Although conventional respiratory metrics focusing on the quantification of the frequency of respiratory events are useful in the diagnosis of SDB, their ability to predict CV outcomes is generally poor, likely reflecting the limitations of a simple index to characterize the complex pathophysiological consequences of SDB on the CV system.[4, 5] Sleep study-derived circulation time (Ct) is a physiological measure that can be measured repeatedly in the presence of apneic episodes accompanying distinct oxygen drop and recovery. A number of studies have demonstrated an inverse correlation between oxygen-based Ct and cardiac output, suggesting Ct as a physiological measure of the CV response to SDB events.[6–8] Physiological measures that reflect the degree of CV stress in response to SDB and indicate underlying CV susceptibility could provide valuable prognostic information. We hypothesized that sleep study-derived lung to finger Ct (LFCT) would improve risk prediction of markers of subclinical CV disease.

We included participants in the Multi-Ethnic Study of Atherosclerosis (MESA) Sleep cohort with moderate-severe SDB (apnea hypopnea index [AHI] ≥ 15 /hr) to allow sufficient number of respiratory events to measure LFCT while also focusing on correlated and predictors related to LFCT in a high risk group. The research protocols were approved by the Institutional Review Boards at each participating institution, and all participants gave written informed consent. Details in MESA Sleep cohort has been previously described.[9] LFCT was defined as the time interval between initiation of breathing (oxygen entry) after an apneic episode and the nadir point of peripheral oxygen saturation.[10] LFCT was measured in an automated fashion using a fiduciary point-based algorithm developed by the investigators.[11] Average LFCT across all respiratory events per subject was analyzed. Subclinical CV markers examined included coronary artery calcification (CAC), carotid intima-media thickness (cIMT) and left ventricular hypertrophy (LVH) and were obtained by cardiac computerized tomography (CT), carotid ultrasound and cardiac magnetic resonance imaging (MRI), respectively, within 1–2 years of MESA Sleep study. High CAC burden was determined by CAC score > 400 by Agatston method.[12] Carotid plaque presence was defined as a focal abnormal wall thickness (IMT > 1.5 mm) or a focal thickening of $> 50\%$ of the surrounding IMT.[12] LVH was determined if left ventricular mass indexed to body surface area was greater than 122 g/m^2 and 149 g/m^2 for women and men respectively.[13] We constructed a general linear regression model designating average LFCT as an independent variable and subclinical CV outcomes of interest as dependent variables. Other covariates including race/ethnicity, hypertension (defined as seated systolic blood pressure (BP) ≥ 140 , diastolic BP ≥ 90 , Sixth Report of the Joint National Committee (1997) criteria), diabetes and LDL lipid medications, smoking and body mass index were included in the model. Another model was constructed by additionally including sleep variables; either

traditional index of sleep apnea severity (AHI or time spent with O₂ saturation below 90%) or degree of sleepiness (Epworth sleepiness scale) in the model. Significance of the association was determined if the p value of the beta coefficient (β) was less than 0.05. Each subclinical CV outcomes of interest was entered in the model separately. Race interaction was tested by including the product of race and each subclinical CV outcomes of interest in the model. Finally, to test the improvement of the risk classification of subclinical CV outcomes by LFCT beyond AHI, we calculated C statistics of the model with and without LFCT.

A total of 598 subjects were included. Those with average LFCT above the median (19.4 sec) (vs. shorter LFCT) tended to be older, less obese and male (Table 1). Subjects with longer average LFCT also had a higher prevalence of LVH, any CAC and heavy CAC.

In multivariable analysis, no significant associations were found between average LFCT and any of subclinical cardiovascular markers (beta coefficient (p value)): Any CAC 0.09 (0.55), High CAC -0.14 (0.35), Carotid plaque -0.02 (0.94), LVH 0.1 (0.69) respectively. The results remained similar in the model that additionally included AHI, time spent with SpO₂< 90% or Epworth sleepiness scale. Moreover, no significant associations were found between each of the sleep variable and any of subclinical CVD (data not shown) No interaction by race or age was found. With regard to C statistics, addition of average LFCT to AHI modestly improved risk prediction of any CAC and heavy CAC as compared with AHI alone (Any CAC: C statistics 0.62 vs. 0.53, p=0.0066; Heavy CAC: C statistics 0.63 vs. 0.52, p=0.0036) (Table 2). In contrast, no risk classification improvement was observed for carotid plaque or LVH (Carotid plaque: C statistics 0.54 vs. 0.52, p=0.63; LVH: C statistics 0.60 vs. 0.58, p=0.99).

In this study, we examined whether sleep study-derived lung to finger Ct (LFCT) would improve risk classification of markers of subclinical CV disease. We found that the risk prediction of any subclinical atherosclerotic CV marker by AHI was poor. Addition of average LFCT modestly improved risk prediction of prevalent CAC. CAC is one of the most established subclinical atherosclerotic CV markers that has high prognostic value in prediction of acute myocardial infarction, stroke and CV death in otherwise healthy individuals. [14] In a previous MESA study, CAC outperformed other CV risk markers including hs CRP, carotid IMT, ankle brachial index, brachial flow-mediated dilation, and family history of CHD in prediction of CHD and CV outcomes.[15] Therefore, considering LFCT in addition to AHI, the single most commonly used SDB metric to determine the severity of OSA, may offer modest advantage in the risk classification of the one of the most well established markers subclinical atherosclerotic CV burden. Despite the improvement in the C-statistics by adding LFCT to AHI, the overall model performance still remained poor. However, considering multifactorial nature of atherosclerotic disease, rather poor prediction by sleep variable alone is not entirely surprising.

OSA has been linked to the increased CAC burden and progression. [16–18] Furthermore, OSA is associated with the increased risk of future CHD, [1, 19] In this context, identification of physiological markers from sleep studies that improve risk classification of CAC, one of the strongest subclinical markers for future risk of CHD, is clinically relevant.

LFCT is a readily measurable from sleep studies including portable sleep studies that measure respiratory excursion and pulse oximetry. In the context of heart failure, prolonged LFCT is regarded as one of the core features of Cheyne Stokes respiration-central sleep apnea. However, its use in patients without heart failure who constitute the majority of people undergoing screening for OSA has been limited due to a paucity of investigations about its relevance.

From a pathophysiological standpoint, based on the knowledge of LFCT's inverse correlation with cardiac output, long average LFCT may be a marker of exposure to a higher degree of increased left ventricular afterload, an important determinant of cardiac output. A higher degree of increased left ventricular afterload for a given OSA severity (by AHI) would be associated with more exaggerated sympathetic and hypertensive response, leading to more accelerated atherosclerotic process in the coronary vasculature. Indeed, hypertension is an important risk factor for CAC development.[20] However, this mechanism does not explain the absence of association or risk classification improvement for LVH. While increased left ventricular afterload may predispose one to LVH, LVH is not a sensitive or specific marker in this regard; studying other diastolic functional parameters in this context could provide more insights into this question. No association was found between LFCT and carotid plaque, which is another predictor of CV disease, particularly cerebrovascular events. [12] It is important to note that risk classification of any subclinical CV markers by AHI alone was poor. Addition of LFCT yielded some improvement in terms of CAC but the overall risk classification remained modest. Despite this, LFCT is readily measurable and thus may contribute to multi-marker models of OSA-related risk. We suppose that LFCT would be particularly useful in the risk prediction of heart failure or outcomes of patients with heart failure in those with sleep apnea but our study sample did not allow us to assess this. Future studies in this aspect would be important. By and large, our findings highlight the need to further investigate other sleep study-related markers that may meaningfully improve the prediction of CVD either alone or in combination with other established risk prediction model.

Our study has several strengths including the objective measurement of sleep characteristics using PSG derived from large community-based multiethnic population. However, because our analysis was cross-sectional, the temporal relationship between LFCT and the development of subclinical CV markers cannot be established. Moreover, significant findings could have resulted from multiple testing and as such, replication using independent cohorts is needed. Future longitudinal studies investigating the utility of the LFCT in the prediction of future risk of CAC, CHD and CV outcomes would be important to validate our study findings.

In conclusion, we report a modest benefit of addition of average sleep study-derived LFCT to traditional SDB metrics in improving the risk classification of CAC, a powerful subclinical atherosclerotic marker of CHD and CV outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the NHBLI, by grants UL1-TR-000040, UL1-RR-025005 from NCRR, R01HL098433 (MESA Sleep), R35HL135818, R21HL140432 and AASM 162-FP-17. This publication was also developed under a STAR research assistance agreements, No. RD831697 (MESA Air) and RD-83830001 (MESA Air Next Stage), awarded by the U.S Environmental Protection Agency. It has not been formally reviewed by the EPA. The views expressed in this document are solely those of the authors and the EPA does not endorse any products or commercial services mentioned in this publication.

References

- [1]. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation*. 2010;122:352–60. [PubMed: 20625114]
- [2]. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378–84. [PubMed: 10805822]
- [3]. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med*. 2010;182:269–77. [PubMed: 20339144]
- [4]. Jonas DE, Amick HR, Feltner C, et al. Screening for obstructive sleep apnea in adults: Evidence report and systematic review for the us preventive services task force. *JAMA*. 2017;317:415–33. [PubMed: 28118460]
- [5]. Punjabi NM. COUNTERPOINT: Is the Apnea-Hypopnea Index the Best Way to Quantify the Severity of Sleep-Disordered Breathing? No. *Chest*. 2016;149:16–9. [PubMed: 26182150]
- [6]. 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. [PubMed: 8756809]
- [7]. 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. [PubMed: 9781980]
- [8]. Kwon Y, Van't Hof J, Roy SS, Bache RJ, Das G. A Novel Method for Assessing Cardiac Output With the Use of Oxygen Circulation Time. *J Card Fail*. 2015.
- [9]. Kwon Y, Gharib SA, Biggs ML, Jacobs DR, Alonso A Jr., Duprez D, et al. Association of sleep characteristics with atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Thorax*. 2015;70:873–9. [PubMed: 25986436]
- [10]. Kwon Y, Khan T, Pritzker M, Iber C. Circulation time measurement from sleep studies in patients with obstructive sleep apnea. *J Clin Sleep Med*. 2014;10:759–65, 65A. [PubMed: 25024653]
- [11]. Kwon Y, Mariani S, Gadi S, Weng J, Jacobs DR, Punjabi N, et al. 0450 Characterization Of Lung To Finger Circulation Time: The Multi-ethnic Study Of Atherosclerosis. *Sleep*. 2018;41:A170–A1.
- [12]. Gepner AD, Young R, Delaney JA, Tattersall MC, Blaha MJ, Post WS, et al. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2015;8.
- [13]. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57:450–8. [PubMed: 2936235]
- [14]. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Intern Med*. 2004;164:1285–92. [PubMed: 15226161]
- [15]. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308:788–95. [PubMed: 22910756]

- [16]. Kwon Y, Duprez DA, Jacobs DR, Nagayoshi M, McClelland RL, Shahar E, et al. Obstructive sleep apnea and progression of coronary artery calcium: the multi-ethnic study of atherosclerosis study. *Journal of the American Heart Association*. 2014;3:e001241.
- [17]. Seo MY, Lee JY, Hahn JY, Ryu G, Hong SD, Dhong HJ, et al. Association of Obstructive Sleep Apnea With Subclinical Cardiovascular Disease Predicted by Coronary Artery Calcium Score in Asymptomatic Subjects. *Am J Cardiol*. 2017;120:577–81. [PubMed: 28645471]
- [18]. Sorajja D, Gami AS, Somers VK, Behrenbeck TR, Garcia-Touchard A, Lopez-Jimenez F. Independent association between obstructive sleep apnea and subclinical coronary artery disease. *Chest*. 2008;133:927–33. [PubMed: 18263678]
- [19]. Hla KM, Young T, Hagen EW, Stein JH, Finn LA, Nieto FJ, et al. Coronary heart disease incidence in sleep disordered breathing: the Wisconsin Sleep Cohort Study. *Sleep*. 2015;38:677–84. [PubMed: 25515104]
- [20]. Lehmann N, Erbel R, Mahabadi AA, Kalsch H, Mohlenkamp S, Moebus S, et al. Accelerated progression of coronary artery calcification in hypertension but also prehypertension. *J Hypertens*. 2016;34:2233–42. [PubMed: 27512973]

Highlights

Lung to Finger Circulation Time in Sleep Study and Coronary Artery Calcification: The Multi-Ethnic Study of Atherosclerosis [Brief Communication]

- Lung to finger circulation time (LFCT) can be measured from sleep study
- Longer LFCT may indicate higher cardiovascular risk in patients with sleep apnea
- LFCT was not significantly associated with subclinical cardiovascular measures
- There was modest improvement in risk classification of coronary artery calcification

Table 1.

Baseline characteristics of the study participants (N=598)

	All (N=598)	Low average LFCT (N=299)	High average LFCT (N=299)	P value
	Mean $\pm$ SD or Freq (%)	Mean $\pm$ SD or Freq (%)	Mean $\pm$ SD or Freq (%)	
Age	69.02 $\pm$ 8.94	67.74 $\pm$ 8.69	70.30 $\pm$ 9.02	0.0004
Sex (male)	362 (60.54%)	151 (50.5%)	211 (70.57%)	<0.001
BMI (kg/m ²)	30.61 $\pm$ 5.87	31.45 $\pm$ 6.16	29.77 $\pm$ 5.43	0.0004
Height (cm)	166.65 $\pm$ 10.08	165.2 $\pm$ 10.16	168.1 $\pm$ 9.8	0.0004
Weight	187.75 $\pm$ 40.73	189.4 $\pm$ 41.01	186.1 $\pm$ 40.44	0.31
Smoking (Current)	33 (5.52%)	20 (6.69%)	13 (4.35%)	0.16
Hypertension (JNC Criteria)	366 (61.31%)	176 (59.06%)	190 (63.55%)	0.26
Systolic BP	124.06 $\pm$ 18.77	123.8 $\pm$ 18.91	124.3 $\pm$ 18.66	0.76
Diastolic BP	69.07 $\pm$ 9.76	68.68 $\pm$ 9.87	69.45 $\pm$ 9.65	0.34
Hypertension medication	346 (57.86%)	165 (55.18%)	181 (60.54%)	0.19
Race, N (%)				0.11
White	196 (32.78%)	93 (31.10%)	103 (34.45%)	
Chinese American	85 (14.21%)	39 (13.04%)	46 (15.38%)	
African American	154 (25.75%)	90 (30.10%)	64 (21.40%)	
Hispanic	163 (27.26%)	77 (25.75%)	86 (28.76%)	
Obstructive AHI	31.68 $\pm$ 16.70	30.32 $\pm$ 16.37	33.05 $\pm$ 16.93	0.05
Mean O ₂ saturation during sleep	93.37 $\pm$ 1.95	93.20 $\pm$ 2.11	93.54 $\pm$ 1.76	0.03
Time spent O ₂ saturation<90%	8.21 $\pm$ 12.26	8.67 $\pm$ 13.96	7.74 $\pm$ 10.29	0.36
Epworth sleepiness scale	6.51 $\pm$ 4.43	6.94 $\pm$ 4.61	6.08 $\pm$ 4.22	0.019
LV hypertrophy	26 (6.68%)	8 (4.10%)	18 (9.28%)	0.04
Any CAC	335 (72.98%)	152 (67.56%)	183 (78.21%)	0.01
Heavy CAC	101 (22.0%)	38 (16.89%)	63 (26.92%)	0.01
Carotid plaque (presence)	327 (70.02%)	159 (69.13%)	168 (70.89%)	0.68

Low vs. High LFCT is based on the median value of 19.4 sec. Comparisons between two groups were made using Rank-Sum test. AHI, apnea hypopnea index; BP, blood pressure; CAC, coronary artery calcification

p-value obtained from student t-test and chi-square, respectively

Table 2.

Model performance in classification of subclinical cardiovascular markers

Outcomes	C-statistics AHI only in the model	C-statistics AHI and average LFCT in the model	p-value (Comparison of C-statistics- AHI and average LFCT compared to AHI only model)
LVH	0.58	0.60	0.32
Any CAC	0.53	0.62	0.0066
Heavy CAC	0.52	0.63	0.0036
Carotid plaque	0.52	0.54	0.63

AHI, apnea hypopnea index; LFCT, lung to finger circulation time; LVH, left ventricular hypertrophy; CAC, coronary artery calcification