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Sleep-disordered breathing and retinal microvascular diameter

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Abstract

Background—Sleep-disordered breathing (SDB) is an emerging risk factor for cardiovascular disease (CVD). Microvascular dysfunction has been proposed as a potential mechanism in the pathogenesis of CVD in SDB. The retinal vasculature offers a unique opportunity to investigate the systemic effects of microvascular dysfunction as it can be viewed non-invasively and is also structurally and functionally similar to microvasculature elsewhere in the body. We therefore examined the association between SDB and retinal microvascular diameter after adjusting for major confounders.

Methods—We examined n=476 participants from the Wisconsin Sleep Cohort Study. SDB was characterized using the apnea-hypopnea index (AHI) as <5 events/hr, 5-14.9 events/hr, and ≥15 events/hr. Outcomes of interest included the presence of retinal arteriolar narrowing (mean retinal arteriolar diameter <141.0 um) and retinal venular widening (mean venular diameter >223.0 um).

Results—Higher AHI was found to be positively associated with retinal venular dilatation, independent of body mass index, hypertension, diabetes, and lipid levels. Compared to an AHI of <5 events/hr (referent), the multivariable-adjusted odds ratio of retinal venular widening for an AHI of 5-14.9 events/hr was 1.31(0.75-2.28) and for an AHI of >15 events/hr was 2.08 (1.03-2.16); p-trend=0.045. In contrast, there was no association between AHI and retinal arteriolar narrowing (p-trend=0.72).

Conclusion—Higher AHI, a marker of SDB, was positively associated with wider retinal venules, independent of age, gender, BMI, hypertension, diabetes, and lipid levels. These data suggest that the association of SDB with cardiovascular disease may be mediated, in part, by microvasculature.

Keywords

SDB; retinal arteriolar diameter; AHI

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Sleep-disordered breathing (SDB) is now recognized to be a common condition estimated to affect 5%-10% of middle-aged adults and 20%-30% of the elderly[1-3]. Studies suggest that SDB is associated with hypertension[4-6], glucose intolerance and diabetes mellitus[7], cardiovascular disease (CVD),[8-10] and higher mortality[11]. However, the mechanistic link between SDB and these conditions remains largely unclear. While previous epidemiological studies have suggested that these associations may reflect increased atherosclerosis and endothelial dysfunction in large-vessels[12-17], emerging evidence from small clinical studies seem to suggest an association between SDB and microvasvcular dysfunction also[18;19]. In this context, there is a need to study the effect of SDB on microvascular dysfunction in larger epidemiological studies.

The retinal vasculature offers a unique opportunity to investigate the microvasculature as it can be viewed non-invasively and also has been shown to be structurally and functionally similar to microvasculature elsewhere in the body[20]. Recent advances in retinal imaging have allowed quantitative measurement of retinal microvascular caliber in large epidemiological studies[20] that have in turn shown that retinal arteriolar diameter is predictive of diabetes mellitus[21], hypertension[21], and CVD[22;23], including coronary heart disease and stroke.

However, only one previous study has examined the association between SDB and retinal microvessel diameter[24]. In that study, Boland et al. used the arteriolar-to-venular ratio (AVR), a summary measure for arteriolar narrowing and venular widening, and found no evidence of an association with SDB[24]. However, subsequent new evidence from retinal imaging studies have advanced the field forward and suggest that arteriolar narrowing and venular widening are two separate pathophysiological processes[25] that should be examined separately, rather than summarizing them in a single ratio measure[26;27]. Therefore, we examined the association between SDB and retinal arteriolar and venular diameters separately in a population-based study from Wisconsin.

METHODS

As described in detail elsewhere[3;28], the Wisconsin Sleep Cohort study (WSCS) was established in 1989 as a population-based sample of Wisconsin state employees between the ages of 30 and 60 years at recruitment. Participants have been followed from 1989 to the present through repeated visits that have included a variety of health questionnaires, laboratory data, and clinical exams, including full overnight polysomnography (PSG). A random subset of 546 participants from the WSCS was selected to participate in an ancillary study to measure additional cardiovascular, and metabolic parameters , including retinal photography between October 2004 and December 2007[29]. The aim of the current analysis was to examine the association between SDB and retinal microvascular diameter. Out of the 546 subjects, we excluded n=55 subjects with missing retinal vessel diameter measurements, or other key covariates, including body mass index (BMI), and lipids, and n=15 additional subjects who were receiving continuous positive airway pressure (CPAP). This resulted in n=476 subjects with complete covariable information available for the current analysis. The parent study and this sub-protocol were approved by the University of Wisconsin-Madison's Health Sciences Institutional Review Board and secondary data analysis by the West Virginia University Institutional Review Board.

SDB was characterized using an 18-channel PSG recording system (16-channel Grass-Telefactor Heritage digital sleep system Model 15, West Warwick, RI). Electroencephalography, electrooculography, and chin electromyography were used to score sleep stage for each 30-sec epoch using standard criteria[30]. Arterial oxyhemoglobin saturation was measured by pulse oximetry (Ohmeda 3740, Englewood, CO, USA). Oral

and nasal airflow were measured using thermocouples (ProTec, Hendersonville, TN, USA). Nasal air pressure was measured with a pressure transducer (Validyne, Northridge, CA, USA). Thoracic cage and abdominal respiratory motion was measured with inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY, USA). These signals were used to identify SDB events. Apnea was defined as cessation of airflow lasting ≥10 sec. Hypopnea was defined as a decrease in tidal volume (plethysmograph signal) accompanied by a ≥4% reduction in oxihemoglobin saturation. The apnea-hypopnea index (AHI) was defined as the average number of apneas plus hypopneas per hour of objectively measured sleep. The PSG study closest in time prior to the ancillary study was used to characterize the participants' sleep. The mean lag time between the sleep study and the ancillary study was 2.2 years (range 0.6-9.6 years).

Details of retinal photography and retinal vessel diameter measurement have been described in detail before[31]. Color retinal photographs of both eyes were taken using a digital nonmydratic retinal camera (CR-DGi with a 10D SLR backing; Canon, Tokyo, Japan). Two retinal images of each eye were obtained, one centered on the Early Treatment for Diabetic Retinopathy Study (ETDRS) standard field 1 (the optic disc) and another centered on the ETDRS standard field 2 (the fovea). Images were sent to the Ocular Epidemiology Research Centre, University of Wisconsin-Madison, for measurement of retinal vascular caliber. For each participant, the images were graded for retinal vessel measurements by using computer-assisted software (IVAN; University of Wisconsin, Madison, Wisconsin) by a trained grader, who was masked to participant characteristics. All arterioles and venules coursing through a specified zone of 0.5 to 1 disc diameter surrounding the optic disc margin were measured and summarized as the central retinal arteriolar equivalent (CRAE) or the central retinal venular equivalent (CRVE) using a modification of the Parr-Hubbard formula[32] as described by Knudtson et al[33]. Reproducibility of these retinal measurements has been previously reported with intragrader and intergrader intraclass correlation coefficients ranging from 0.78 to 0.99[34]. For the current analysis, average of the right and left eye measurements were taken as the retinal arteriolar diameter (average CRAE) and the retinal venular diameter (average CRVE) value for each participant.

BMI was calculated as weight (kg) divided by height (meters) squared. Serum fasting glucose, triglycerides and high-density lipoprotein (HDL) cholesterol were measured at the University of Wisconsin Hospital clinical laboratory using standard methods. Diabetes mellitus was defined based on the guidelines of the American Diabetes Association as a serum glucose >126mg/dl after fasting for a minimum of 8 hours or a self-reported current use of oral hypoglycemic medication or insulin. Subjects were considered hypertensive if they reported current blood pressure-reducing medication use and/or had systolic blood pressures >140 mm of Hg and/or diastolic blood pressures >90 mm of Hg.

Statistical analysis

Chi-square test and analysis of variance were used to compare proportions and means, respectively. SDB was categorized as no SDB (AHI <5 events/hr), mild SDB (5-14.9 events/hr), and moderate/severe SDB (≥15 events/hr)[29]. The main outcome of interest was retinal microvascular diameter, including retinal arteriolar narrowing and retinal venular widening. We analyzed retinal microvascular diameter as a continuous as well as categorical variable. First, we examined the association between increasing SDB categories and retinal venular and arteriolar diameters in separate multivariable linear regression models. Second, we examined the association between increasing SDB categories and the presence of retinal venular widening (defined as having CRVE in the highest quartile, >223.0 um) and retinal arteriolar narrowing (defined as having CRAE in the lowest quartile, <141.1 um) in separate multivariable logistic regression models. For both the linear as well as logistic regression, we employed two nested models: the first one adjusted for age (years), sex (men, women),

race-ethnicity (whites, non-whites), and the fellow retinal vessel diameter (um) to adjust for magnification artifacts[32], refractive errors[35], and confounding by the fellow vessel as recommended by Liew et al.[26;27]; and the second one additionally adjusted for smoking (never, former, current), alcohol intake (drinks/week), body mass index (kg/m^2), diabetes (absent, present), serum low-density lipoprotein cholesterol (mg/dL), and serum high-density lipoprotein cholesterol (mg/dL). We also performed the following supplementary analyses: 1) we additionally adjusted for hypertension (yes, no) to examine if the association between SDB and microvascular diameter was independent of the mediating effect of hypertension; 2) we ran the multivariable linear regression model using AHI and retinal vessel diameters as continuous variables to examine if the results are similar without AHI categorization; and 3) we included CPAP users in the analysis and grouped them as subjects with moderate/severe SDB and reran the multivariable models to see if the results changed. For the multivariable linear regression, we ran models with log transformation of AHI and retinal vessel diameters as well as without log transformation. Since the overall conclusions were essentially similar, we chose to present the untransformed analysis as it allows a more direct interpretation. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Table 1 presents the baseline characteristics of the study sample by severity of SDB, as measured by increasing AHI categories. Subjects with higher AHI values were older, more likely to have a higher BMI, diabetes mellitus, lower serum high-density lipoprotein cholesterol; and less likely to be women.

Table 2 presents the association between increasing AHI categories and mean change in retinal venular and arteriolar diameter (in um) in separate models. We observed a positive association between increasing AHI categories and mean change in retinal venular diameter. In contrast, there was no association between increasing AHI categories and change in mean retinal arteriolar diameter.

Table 3 presents the association between increasing AHI categories and the presence of retinal venular widening (defined as having CRVE in the 4th quartile, >223.0 um) and retinal arteriolar narrowing (defined as having CRAE in the 1st quartile, <141.01 um) in separate models. Similar to the results in Table 2, here also we found that increasing AHI categories were positively associated with retinal venular widening but not with arteriolar narrowing.

We also performed several supplementary analyses. First, we included hypertension (absent, present) in the multivariable model; the results were slightly attenuated, but the overall findings remained unchanged. For example, compared to an AHI of <5 events/hr (referent), the multivariable-adjusted odds ratio (95% confidence interval) of retinal venular widening for an AHI of 5-14.9 events/hr was 1.28 (0.74-2.21) and for an AHI of >15 events/hr was 1.97 (1.00-3.88); p-trend=0.054. In contrast, there was no association between AHI and retinal arteriolar narrowing (p-trend=0.70). Second, we ran a multivariable linear regression model using AHI and retinal vessel diameters as continuous variables. Here also SDB was found to be positively associated with retinal venular diameter but not with retinal arteriolar diameter. For retinal venular diameter, the multivariable-adjusted beta coefficient (standard error) was 0.14 (0.07), p=0.043; and for retinal arteriolar diameter it was -0.05 (0.007), p=0.15. Third, we included CPAP users also in the analysis and reran the models; the results were found to be essentially similar. Fourth, we examined the relation between AHI and retinal venular widening separately among normal weight(BMI <25 kg/m^2) and overweight/obese (BMI ≥25 kg/m^2) subjects. One unit increase in AHI was associated with a

multivariable-adjusted odds ratio of 1.28 (1.07-1.53) in the whole study sample, 1.41 (1.10-1.81) in normal weight subjects, and 1.20 (1.01-1.43) in overweight/obese subjects. In contrast, when we repeated the same analysis with retinal arteriolar narrowing as the outcome, there was no association between AHI and retinal arteriolar narrowing in normal weight (p-value=0.49) or overweight/obese subjects (p-value=0.65).

DISCUSSION

In a population-based study of middle-aged subjects from Wisconsin, we found that higher AHI, a measure of SDB severity, was positively associated with retinal venular dilatation, independent of age, gender, BMI, diabetes, and serum lipid levels. In contrast, the association between AHI and retinal arteriolar narrowing was weak and not statistically significant. Our results contribute to the emerging literature on the role of SDB on cardiovascular[9-11] and metabolic diseases[7] by suggesting that at least part of this association may be mediated by microvasculature.

SDB is now recognized to be a common condition[1-3]. Several epidemiological studies have reported an association between SDB and hypertension[5;6;29], diabetes mellitus[7], cardiovascular disease[9-11], subclinical CVD measures such as carotid inti mamedia thickness[13], and higher mortality[11]. Previous studies have suggested that large vessel atherosclerosis and endothelial dysfunction may have a role in the development of CVD in relation to SDB[12;14-17]. However, it is not clear whether SDB is associated with similar pathogenetic changes in systemic microvasculature. It has been shown that retinal microvasculature is structurally and functionally similar to cerebral vasculature with the important added advantage of being available for non-invasive visualization[20;31]. Therefore, imaging studies of retinal microvasculature such as ours provide a unique opportunity to study the microvascular effects of SDB in humans[20].

Retinal microvessels are composed of arterioles and venules which may have different pathophysiological antecedents and sequelae[20;25]. Recent studies have shown that narrower retinal arterioles are associated with hypertensive changes whereas wider retinal venules with inflammation, metabolic abnormalities, higher glycosylated hemoglobin levels and impaired fasting glucose[25]. Therefore, from a pathophysiological point of view, it important to study the association between SDB and retinal arteriolar and venular diameters separately[27].

To date, only one study has examined the association between SDB and retinal microvascular diameter[24]. That study used AVR, a summary measure for arteriolar narrowing and venular widening, and found no evidence of an association with SDB[24]. However, summarizing arteriolar and venular diameters in a single ratio measure may mask important mechanistic insights as they denote separate pathophysiologic changes[25-27]. The same AVR value may result from a narrow or wide arteriolar diameter as long as the ratio with venular diameter is the same. Liew et al. showed that the use of AVR in a regression equation involves making the wrong *a priori* assumption that the beta coefficient for arteriolar caliber is equal in magnitude, but opposite in sign, to the coefficient for venular caliber[27]. Subsequently, it has been recommended to avoid using AVR in retinal imaging studies and to examine arteriolar and venular diameters separately[27]. It is in this context that our results are important. We found that when analyzed separately, higher AHI was positively associated with retinal venular widening, independent of confounders. In contrast, AHI was not associated with retinal arteriolar narrowing. Also, our findings of an association between retinal venular widening and AHI (defined as respiratory events associated with with >4% oxygen desaturation in sleep) are analogous to findings by de

Jong et al. showing an association between oxygen desaturation measured during waking hours by pulse oximetry and retinal venular widening in the Rotterdam Study[36].

These contrasting findings indirectly suggest that SDB may be related to microvasculature through inflammation, metabolic abnormalities, and dysglycemia, factors that are known to be related to retinal venular widening[25], rather than through high blood pressure, which is associated with retinal arteriolar narrowing[25].

Advantages of our study include its population-based nature, availability of standardized polysomnography measures at a controlled sleep lab, and the availability of data on confounders. The main limitation is the cross-sectional nature of the study which limits our ability to draw conclusions regarding the temporal nature of associations observed. Also, these data are derived from a group of mostly Causacian adults and may differ in non-white persons.

In summary, in a population-based study, we found that higher AHI, a marker of SDB, was positively associated with retinal venular widening, independent of age, gender, BMI, diabetes, and lipid levels. Therefore, microvascular dysfunction may be a mechanism by which SDB is associated with elevated cardiovascular risk.

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- We examined the relationship between SDB markers and retinal mivrovascular diameters.
- Higher apnoea-hypopnea indes (AHI) was found to be associated with retinal venular dilatation.
- In contrast, there was no association between AHI and retinal arteriolar narrowing.

Table 1

Characteristics of the population by sleep disordered breathing (SDB) severity

Characteristics	No SDB (AHI: <5 events/hr)	Mild SDB (AHI: 5-14.9 events/hr)	Moderate SDB (AHI: ≥15 events/hr)	P-value
Sample size	251	156	69	
Age (years)	58.9±0.5	61.2±0.6	60.4±0.9	0.01
Women (%)	50.2	35.9	39.13	0.01
Race-ethnicity, %				
Whites	97.2	97.4	97.1	0.99
Non-Whites	2.8	2.6	2.9	0.99
Alcohol intake, drinks/week	3.9±0.3	4.2±0.4	3.4±0.6	0.50
Body mass index, kg/m^2	28.5±0.4	31.5±0.5	35.2±0.7	<0.0001
Diabetes mellitus, %	7.6	16.0	20.3	0.001
Low-density lipoprotein cholesterol, mg/dL	115.6±2.2	116.4±2.8	111.7±4.3	0.65
High-density lipoprotein cholesterol, mg/dL	61.6±0.9	56.4±1.2	54.6±1.8	0.0001

* Data presented are row percentages or mean values ± standard error (SE)

Table 2

Association between sleep-disordered breathing (SDB) and change in retinal arteriolar and venular diameter

SDB categories by apnea-hypopnea index (AHI)	Sample size	Mean retinal arteriolar diameter in um	Change in mean retinal vessel diameter (95% CI) from multivariable model 1 in um*	Change in mean retinal vessel diameter (95% CI) from multivariable model 2 in um†
Retinal venular diameter				
No SDB (AHI: <5 events/hr)	251	210.4	0 (Referent)	0 (Referent)
Mild SDB (AHI: 5-14.9 events/hr)	156	211.1	0.69 (−2.41, 3.78)	0.70 (−2.41, 3.81)
Moderate SDB (AHI: >15 events/hr)	69	215.1	4.92 (1.12, 8.73)	4.71 (0.75, 8.68)
p-trend			0.021	0.034
Retinal arteriolar diameter				
No SDB (AHI: <5 events/hr)	251	147.9	0 (Referent)	0 (Referent)
Mild SDB (AHI: 5-14.9 events/hr)	156	147.3	−0.88 (−3.06, 1.31)	−0.58 (−2.82, 1.66)
Moderate SDB (AHI: >15 events/hr)	69	145.9	−2.40 (−5.10, 0.30)	−1.98 (−4.64, 0.84)
p-trend			0.08	0.19

*Adjusted for age (years), sex (men, women), race-ethnicity (whites, non-whites), fellow retinal vessel diameter (um)

†Additionally adjusted for smoking (never, former, current), alcohol intake (drinks/week), body mass index (kg/m^2), diabetes (absent, present), serum low-density lipoprotein cholesterol (mg/dL), serum high-density lipoprotein cholesterol (mg/dL)

Table 3

Association between sleep-disordered breathing (SDB) and retinal arteriolar narrowing or venular widening

SDB categories by apnea-hypopnea index (AHI)	Sample size	No. with retinal arteriolar narrowing or venular widening	Odds ratio (95% CI) from multivariable model 1*	Odds ratio (95% CI) from multivariable model 2†
Retinal venular widening defined as CRVE>223.0 um				
No SDB (AHI: <5 events/hr)	251	79	Referent	Referent
Mild SDB (AHI: 5-14.9 events/hr)	156	52	1.33 (0.79, 2.24)	1.31 (0.75, 2.28)
Moderate SDB (AHI: >15 events/hr)	69	29	2.17 (1.13, 4.20)	2.08 (1.03, 2.16)
p-trend			0.022	0.045
Retinal arteriolar narrowing defined as CRAE<141.1 um				
No SDB (AHI: <5 events/hr)	251	81	Referent	Referent
Mild SDB (AHI: 5-14.9 events/hr)	156	53	1.00 (0.61, 1.65)	0.93 (0.54, 1.60)
Moderate SDB (AHI: >15 events/hr)	69	25	1.38 (0.74, 2.58)	1.19 (0.61, 2.32)
p-trend			0.39	0.72

*Adjusted for age (years), sex (men, women), race-ethnicity (whites, non-whites), fellow retinal vessel diameter (um)

†Additionally adjusted for smoking (never, former, current), alcohol intake (drinks/week), body mass index (kg/m^2), diabetes (absent, present), serum low-density lipoprotein cholesterol (mg/dL), serum high-density lipoprotein cholesterol (mg/dL)