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Impact of Sleep Disordered Breathing on Carotid Body Size

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Abstract

We tested the hypotheses that: 1) carotid body size can be measured by computed tomographic angiography (CTA) with high inter-observer agreement, and 2) patients with sleep apnea exhibit larger carotid bodies than those without sleep apnea. A chart review was conducted from patients who underwent neck CTA and polysomnography at the Mayo Clinic between January 2000 and February 2015. Widest axial measurements of the carotid bodies, performed independently by two radiologists, were possible in 81% of patients. Intra-class correlation coefficients ranged from 0.93 to 0.95 (Right carotid body: 0.93; Left: 0.94; Average: 0.95). Widest axial measurements of the carotid bodies were greater in patients with sleep apnea (n=32) compared to controls (n=46, *P*-value range 0.02–0.04). After adjusting for age, no differences in carotid body size were observed between the patient groups (*P*-value range 0.45–0.59). We conclude carotid body size can be detected by CTA with high inter-observer agreement; however carotid body size is not increased in patients with sleep apnea.

Keywords

Sleep apnea; Apnea Hypopnea Index; Computed tomography angiography; Hypoxemia

1. INTRODUCTION

The carotid body chemoreceptors are located bilaterally at the bifurcation of the common carotid artery and are thought to be the body's primary oxygen sensors (Kumar and Prabhakar, 2012). The carotid body chemoreceptors respond to changes in the partial pressure of oxygen, such that a fall in arterial oxygen levels results in an increase in carotid body afferent activity and subsequently ventilation and sympathetic nervous system activity (Kumar and Prabhakar, 2012). Patients with sleep disordered breathing [clinically defined as an Apnea Hypopnea Index (AHI) of ≥30 events per hour] experience repeated intermittent

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ETHICAL STANDARDS

All procedures were approved by the Mayo Clinic Minimal Risk Institutional Review Board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

CONFLICTS OF INTEREST

All authors report no conflicts of interest.

hypoxic exposures at night and are at increased risk for heart disease, hypertension, diabetes, and related cardiovascular diseases (Herrscher et al., 2014). Tonic activity of the carotid body chemoreceptors is known to be increased in hypoxic conditions such as sleep apnea and recent evidence suggests that increased carotid body chemoreflex activity is a major driver of sympathetic activation in such conditions (Prabhakar, 2016). Furthermore, individuals with increased carotid chemoreceptor activity exhibit increased morbidity and mortality when compared to individuals with relatively low chemoreceptor activity (Ponikowski et al., 2001).

Long-standing evidence from patient populations has shown that those individuals who exhibit chronic hypoxemia also exhibit increased carotid body volume and/or carotid body hyperplasia (Arias-Stella and Valcarcel, 1976; Cramer et al., 2014; Habeck, 1986; Heath and Smith, 1994; Vinhaes et al., 2002). Such conditions include, but are not limited to: acute respiratory disease syndrome (Vinhaes et al., 2002), pulmonary emphysema (Heath and Smith, 1994), chronic obstructive pulmonary disease (Vinhaes et al., 2002), patients with severe lung diseases (Habeck, 1986), and high altitude natives (Arias-Stella and Valcarcel, 1976). The majority of our understandings of carotid body hypertrophy in patients with long-standing hypoxemia are from post-mortem analyses. The post-mortem nature of these assessments has understandable limitations to our ability to adequately interpret the clinical relevance of such results. However, recent work suggests the carotid body may be visible in up to 80% of normal adults undergoing computed tomography angiography (CTA) (Cramer et al., 2014; Nair et al., 2013). Thus, CTA has emerged as a potential new way to assess carotid body size in living individuals.

Carotid body resection was pursued in the 1960s for the treatment of dyspnea in patients with chronic obstructive pulmonary disease; however, its success was limited – likely due to poor patient selection (Joyner and Limberg, 2016). Recently, there has been renewed interest in the carotid chemoreceptors as a potential therapeutic target for conditions related to tonic activity of the carotid body (Paton et al., 2013). With this, CTA may provide an important screening tool to help identify individuals who exhibit increased carotid body size and may benefit from procedures such as carotid body denervation or resection. Using neck CTA, recent data suggest patients with diabetes mellitus, hypertension, and congestive heart failure exhibit a 20–25% larger mean carotid body size when compared with controls (Cramer et al., 2014). With this in mind, we sought to examine whether carotid body size detected by CTA would be increased in individuals with diagnosed sleep disordered breathing. Thus, the purpose of the present investigation was to test the hypotheses that: 1) Carotid body size can be identified by CTA with high inter-observer agreement, and 2) Carotid body size as measured by CTA is greater in individuals with diagnosed sleep apnea when compared to controls.

2. METHODS

2.1. Approval

All procedures were approved by the Mayo Clinic Minimal Risk Institutional Review Board.

2.2. Patients

A retrospective chart review was conducted from patients at the Mayo Clinic who were seen between January 2000 and February 2015 that completed the following exams: 1) head/neck CTA, 2) Polysomnography. The clinical indication for CTA imaging was variable and not performed for isolated carotid body analysis, while the clinical indication for Polysomnography was for the diagnosis and assessment of sleep apnea. The protocols for both clinical measurements (CTA and Polysomnography) followed institutional standardization (see below “**2.3. CTA and Carotid Body Measurement**”).

The initial review resulted in 583 patients (See Figure 1). Demographic data (age, sex, height, weight, resting heart rate and blood pressure) were extracted from medical visits surrounding (± 10 weeks) the CTA visit. Subjects were excluded if: 1) the CTA was not performed at Mayo Clinic (n=27), 2) CTA images were not on record (n=2), 3) the subject was <18 years of age at the time of either exam (n=3), 4) the subject could not be identified by their Mayo Clinic identification number (n=8). Clinical data from the electronic medical record were also collected for all patients to exclude potential confounding comorbidities that could impact carotid body size independent of sleep disordered breathing [Type 2 Diabetes, n=114; Heart Failure, n=95; Type 2 Diabetes and Heart Failure, n=42; Type 1 Diabetes, n=7; Type 1 Diabetes and Heart Failure, n=2, (Cramer et al., 2014; Nair et al., 2013)]. Comorbid conditions were extracted based upon physician completion or billing code.

Data from 283 patients were then collected from the Polysomnography exam, including: total sleep duration, AHI, lowest saturation during REM/NREM sleep, average duration of apneic events, and percentage of time during sleep (%TST) spent between 80 and 89% oxygen saturation (S_pO_2). Hypopneas were scored using the American Academy of Sleep Medicine recommended guidelines (Berry et al., 2015). Subjects were excluded if data from the polysomnography exam were incomplete (n=8), if CPAP was administered during the exam (n=9), if total sleep time (TST) was less than 120 minutes (n=10), or if polysomnography was completed >10 years before/after the CTA (n=6). See Figure 1.

Following this, 250 subjects were identified as meeting the above criteria. Subjects were then divided into Low AHI (AHI <5 events/hour; n=53), Intermediate AHI (5 AHI < 30 events/hour; n=141) and High AHI (AHI $\geq$ 30 events/hour; n=56) groups using clinical cut-offs (Herrscher et al., 2014). Given our interest in comparing individuals with sleep disordered breathing to healthy controls, subjects in the “Intermediate AHI” group (n=141) were excluded from further analysis. Widest axial measurements of left and right carotid bodies were then performed by two independent radiologists at the Mayo Clinic Radiology Department, using the images captured during the CTA.

In all subsequent analyses, subjects with an at-home CPAP compliance rate of $\geq$ 80% (n=10, “High AHI” group) were also excluded to ensure assessment of the impact of hypoxic exposure on observed carotid body size. CPAP compliance (as reported in the medical chart) was calculated from nightly use data downloaded from each patient’s CPAP machine during follow-up visits.

2.3. CTA and Carotid Body Measurement

CT algorithms are standardized for carotid angiography at the Mayo Clinic. CTA acquisitions were performed for multiple clinical indications in the outpatient, inpatient, and emergency settings. Bolus tracking was performed on all acquisitions. Posterior/anterior (PA) and lateral topograms were obtained at 120 kV and 100 mA. Pre-monitoring scans were obtained at the level of the proximal ascending aorta. Spiral acquisitions with a pitch of 0.7 were utilized. Kilovoltage was set at 120 with a standard milliampere-second value of 300 and a CARE bolus of 100 mL iodinated contrast at a rate of 4 cc/sec was administered. Post imaging reconstructions were obtained in the axial and coronal plane using a B40 kernel. Slice thicknesses of 0.75 mm and 1.5 mm were reconstructed and maximal intensity projections in the axial, coronal, and sagittal planes were completed with a slice thickness of 6.5 mm and a reconstruction increment of 2.5 mm.

Widest axial measurements of left and right carotid bodies were performed independently by two radiologists (BTW, WB), blinded to patient disease condition using General Electric's Centricity picture archiving and communications system (PACS) following a standardized protocol. In the axial plane, maximum dimensions of the carotid body, if present, were determined using electronic calipers and measurements were reported to the closest millimeter. Carotid body measurement was not performed in 21 patients due to inability to identify the carotid bodies, confounding variables (e.g. carotid body tumor), artifact, or motion (in consensus by both observers). When bilateral measurement was possible (n=67), each radiologist reported both a left and a right carotid body size for each patient and average carotid body size $[(\text{Left} + \text{Right}) \div 2]$ was calculated. When only unilateral measurement was possible (n=21; as a result of low quality CTA image on the opposite side), both radiologists reported either the right (n=6) or left (n=15) carotid body size. The left, right, and average carotid body sizes from each radiologist were utilized for inter-observer variability analyses. Each measure (left, right, average) was then averaged between radiologists for final measures of carotid body size $[(\text{Radiologist \#1} + \text{Radiologist \#2}) \div 2]$.

2.4. Statistical Analysis

All statistical analyses were performed using the R statistical programming software (Version 3.2.2, R Foundation for Statistical Computing, Vienna, Austria). Significance was determined *a priori* at an $\alpha=0.050$ level. All data are expressed as mean $\pm$ standard error of the mean (SEM). Subject demographics are provided in Table 1 and were compared using two-tailed *t*-tests for normally distributed data (Shapiro-Wilk). For non-normally distributed data, comparisons were made using the Mann-Whitney Rank Sum test. To assess the inter-observer carotid body measurement reliability, the intra-class correlation coefficient (ICC) was calculated from the variance components of a two-way mixed effects model. Because groups (High AHI, Low AHI) differed significantly in age and systolic blood pressure, an analysis of covariance (ANCOVA) was performed with carotid body size as the dependent variable (left, right, average) and High AHI/Low AHI as explanatory variables. The analysis was then adjusted for age, systolic blood pressure, diastolic blood pressure, or body mass index (BMI) (Table 2). This analysis resulted in a significance value for the dependent variable (left, right, or average carotid body size) corresponding to a detected difference between groups (with significance set at $p<0.050$).

A *post hoc* exploratory analysis was also conducted to examine the potential effect of S_pO_2 during sleep on carotid body size (See Supplemental Table S1 for group demographics). To do this, the percentage of total sleep time (%TST) spent at an S_pO_2 between 80 and 89% was assessed, and subjects were divided into “High” hypoxic exposure (>5 %) or “Low” hypoxic exposure (<5%) groups (Cooper et al., 1991; Williams et al., 1991). A second ANCOVA was performed with carotid body size as the dependent variable and High S_pO_2 /Low S_pO_2 as explanatory variables and the analysis was adjusted for age, systolic blood pressure, diastolic blood pressure, or BMI (Table 2).

3. RESULTS

3.1. Patients

Carotid body identification was possible in 88 of 109 patients (81%). More specifically, carotid body measurement was possible in 46 out of 53 patients in the Low AHI group (87%) and 42 out of 56 patients in the High AHI group (75%, Figure 1). After excluding patients with a CPAP compliance rate of <80% (n=10, High AHI group; Figure 1), subsequent analyses were conducted on data from 46 patients in the Low AHI group and 32 patients in the High AHI Group (Table 1). Adults in the High AHI group were older at the time of CTA ($p<0.001$) and had higher systolic blood pressure ($p=0.027$) when compared to the Low AHI group (Table 1). Height, weight, and BMI did not differ between the groups ($p>0.050$, Table 1).

3.2. Inter-observer variability

The ICC coefficient for average carotid body diameter measurements was 0.946 with an F-value of 18.5 and a 95% confidence interval for the ICC population value of $0.915 < ICC < 0.965$ ($p<0.001$). The ICC coefficient for the right carotid body measurements was 0.930 with an $F=14.3$ ($0.885 < ICC < 0.957$; $p<0.001$) and the ICC for the left carotid body was 0.943 with an $F=17.5$ ($0.909 < ICC < 0.964$; $p<0.001$).

3.3. Carotid body size by group

In the unadjusted analysis, patients in the High AHI group exhibited larger carotid bodies (right, left, average) when compared to the Low AHI group (Figure 2). However, after adjusting for age, there were no differences observed in right, left, or average carotid body size between patients in the High AHI group and patients in the Low AHI group (Table 2, $p>0.050$). Similarly, after adjusting for BMI or systolic blood pressure, there was no difference in left carotid body size between patients in the High AHI group and patients in the Low AHI group (Table 2, $p>0.050$). After controlling for diastolic blood pressure, left carotid bodies remained larger in patients in the High AHI group as compared to patients in the Low AHI group ($p=0.049$). Additionally, right and average carotid bodies remained larger in patients in the High AHI group after controlling for BMI, systolic blood pressure, or diastolic blood pressure (Table 2, $p<0.050$).

An exploratory analysis was conducted *post hoc* to examine the potential effect of S_pO_2 during sleep on carotid body size by stratifying patients based on the percentage of TST spent at an S_pO_2 between 80 and 89% (%TST S_pO_2 80–89%; High %TST >5%, Low %TST

5%) (Supplemental Table S1). In this case, patients who spent >5% of their TST with pulse oximetry readings between 80–89% (“High” hypoxic exposure) had larger carotid bodies when compared with patients who spent ≤5% of the TST in the same S_pO_2 saturation range (“Low” hypoxic exposure), even after controlling for age (Figure 2, Table 2). However, this was specific to the left carotid body ($p=0.014$), with no differences observed in right or average carotid body size (P -value range 0.134 to 0.793). Similarly, after adjusting for BMI or blood pressure, there were no differences in right carotid body size between patients in the High and Low groups (Table 2, $p>0.050$; however, the High (>5%) group exhibited larger left and average carotid bodies when compared to patients in the Low (≤5%) group (Table 2, $p<0.050$).

4. DISCUSSION

The major findings from the present study are two-fold: 1) Carotid body size can be identified by CTA with ~80% visualization and high inter-observer agreement, and 2) Adults with diagnosed sleep apnea (AHI ≥30 events per hour) do not have larger carotid bodies when compared to healthy adults (AHI <5 events per hour), after controlling for age. Interestingly, when patients were evaluated *post hoc* based on the percentage of total sleep time (TST) spent between 80 and 89% S_pO_2 , carotid body size was greater in the “High” hypoxic exposure group when compared to the “Low” exposure group. These data highlight our ability to visualize carotid body size with CTA in living individuals and support a role for hypoxemia in increased carotid body volume and/or carotid body hyperplasia.

As noted above, our data confirm previous work that carotid body size can be identified by CTA in approximately ~80% of patients (Cramer et al., 2014; Nair et al., 2013). Although previous work suggested CTA may be a valid way to assess carotid body size in living individuals (Cramer et al., 2014; Nair et al., 2013), results were limited by their lack of inter-observer variability analyses, low power, and lack of control for confounding variables when comparing/contrasting heterogeneous patient cohorts (e.g. age, body size, blood pressure, etc). In this context, our findings show high inter-observer agreement (Intra-class correlation coefficients ranging from 0.93 to 0.95). Additionally, we found that individuals with High AHI exhibit ~15% larger carotid bodies when compared to adults with Low AHI. Although carotid body size was shown to be greater in individuals with diagnosed sleep apnea, the causal relationships remain somewhat unclear, given a hyperactive carotid body may contribute to disease progression and/or certain diseases may cause increases in carotid body size. In this way, post mortem analysis provides little understanding of this issue. Alternatively, identifying carotid body size via technically optimized CTA imaging may provide us with the ability to monitor disease activity, therapeutics, and/or identify patients at elevated risk for related morbidity/mortality.

The present analysis was conducted retrospectively; thus, we were unable to experimentally control for differences in age and/or blood pressure between groups. When these factors were controlled statistically, any group differences in carotid body size were attenuated. These findings are consistent with data from rodents exposed to chronic intermittent hypoxia (Del Rio et al., 2011) and suggest that the increased chemoreflex function reported in these

animals and in patients with severe sleep apnea is not due to morphological changes in the carotid body tissue.

As noted above, although adults with High AHI may exhibit larger carotid bodies, this effect was not greater than the impact of age. Consistent with this, previous post-mortem studies have shown an effect of aging on carotid body size. For example, Lack (1977) showed a strong correlation ($r=0.73$, $p<0.001$) between carotid body weight and age in younger (28 weeks to 30 years) individuals and Habeck (1986) observed age-dependent changes in carotid body size, with the largest glomera carotici occurring at age 40–60 years. The influence of age highlights the need for studies that control for this and other potentially confounding variables (e.g. blood pressure) before CTA assessment can be considered as a screening tool.

We also stratified patients based on nocturnal S_pO_2 in an exploratory *post hoc* analysis, with the thought that hypoxia caused by repeated nighttime apneic events could be driving increased carotid body volume and/or carotid body hyperplasia. We found patients who spent >5% of their total sleep time (TST) with pulse oximetry readings between 80–89% (High %TST) had significantly larger carotid bodies when compared with patients who spent ≤5% of their TST in the same S_pO_2 saturation range (Low %TST), even after controlling for age. However, this finding was specific to the left carotid body. This may be a coincidence; however, it is also possible physiological differences exist between the right and left carotid bodies, thus influencing carotid body size in response to acute and/or chronic hypoxic exposures. Consistent with this, work from Williamson and colleagues (1996) suggests that “afferent input from the left carotid sinus may have a greater influence on efferent muscle sympathetic outflow than the right” and trends toward larger carotid bodies on the left versus right side have been reported by other groups (Cramer et al., 2014; Nair et al., 2013). While our understanding of the precise mechanisms that initiate and control cellular hypertrophy and hyperplasia in the carotid body are limited, previous work in animal models has implicated important roles for cAMP (Nurse, 1995). More recent work has highlighted the hypoxia-inducible factor pathway (Slingo et al., 2014) and an O_2 -sensitive glomus cell-stem cell synapse (Platero-Luengo et al., 2014) as potential contributors. Whether such mechanisms can be isolated to one or both carotid bodies has yet to be examined. However, given individuals with heart failure exhibit larger carotid bodies as assessed by CTA (Cramer et al., 2014; Nair et al., 2013), it is likely the causes and consequences of carotid body hypertrophy and/or hyperplasia (e.g. Cheyne-Stokes respiration) are variable across conditions.

4.1. Experimental considerations

The present study was conducted retrospectively; therefore CTA acquisitions were not optimized for carotid body identification. To limit variability and increase reliability of the technique, we utilized maximal axial diameter measurements for carotid body size assessment (Cramer et al., 2014); however, others have relied on volumetric analyses (Nair et al., 2013). Although volumetric tools for size assessment are limited at this time, there is no literature consensus on the most accurate technique for carotid body measurement. It is also important to note that Janzer & Schneider (1977) have shown both carotid body

hypertrophy and hyperplasia occur in response to chronic hypoxemia; hypertrophy at earlier stages and nodular hyperplasia at later stages. It is not possible to distinguish between the two using CTA imaging, and therefore we are unable to comment on which may be contributing to any increases in carotid body size in the present cohort.

5. CONCLUSIONS

In summary, we demonstrate excellent carotid body identification (~80%) with CTA and high ICC coefficients among interpreting radiologists. Present findings also show that although carotid body size is increased in patients with diagnosed sleep disordered breathing, this difference is mitigated when controlling for age. While other studies have documented trends towards carotid body hypertrophy in similar chronic disease states, future studies with appropriate control for confounding variables and comorbidities, including age, are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Subject selection.

Fig. 2. Difference in carotid body size between groups

A: High AHI vs Low AHI. Low AHI (Right, n = 37; Left, n = 42; Average, n = 33). High AHI (Right, n = 28; Left, n = 30; Average, n = 26). **B: High % TST vs Low % TST.** Low %TST (Right, n = 43; Left, n = 49; Average, n = 40). High %TST (Right carotid body, n = 22; Left carotid body, n = 23; Average, n = 19).

Table 1
Subject demographics (Low AHI versus High AHI)

Data are reported as Mean $\pm$ SEM. Low AHI: n = 46 unless otherwise noted (AHI – REM and REM – Low, n = 41). High AHI: n = 32 unless otherwise noted (AHI – REM and REM – Low, n = 25). Bolded values highlight significance.

	Low AHI	High AHI	P-value
<i>Demographics</i>			
Sex	59% M	66% M	
Age at CT (years)	50 $\pm$ 2	65 $\pm$ 2	<0.001
Height (cm)	174 $\pm$ 2	169 $\pm$ 2	0.051
Weight (kg)	89 $\pm$ 3	91 $\pm$ 3	0.697
Body Mass Index (kg/m ²)	30 $\pm$ 1	32 $\pm$ 1	0.145
Systolic Blood Pressure (mmHg)	128 $\pm$ 3	138 $\pm$ 3	0.027
Diastolic Blood Pressure (mmHg)	74 $\pm$ 2	78 $\pm$ 2	0.116
<i>Polysomnography</i>			
Age at Polysomnography (years)	48 $\pm$ 2	65 $\pm$ 2	<0.001
AHI – TST (events/hour)	2 $\pm$ 0	48 $\pm$ 3	<0.001
AHI – NREM (events/hour)	1 $\pm$ 0	47 $\pm$ 3	<0.001
AHI – REM (events/hour)	4 $\pm$ 1	50 $\pm$ 7	<0.001
Mean duration of Apnea Hypopnea (sec)	18 $\pm$ 1	21 $\pm$ 1	0.021
NREM – lowest saturation (% S _p O ₂)	90 $\pm$ 0	81 $\pm$ 1	<0.001
REM – lowest saturation (% S _p O ₂)	90 $\pm$	81 $\pm$ 2	<0.001
% TST at S _p O ₂ 80–89%	1 $\pm$ 0	15 $\pm$ 2	<0.001

Table 2
Difference in carotid body size between groups (High AHI vs Low AHI; High %TST vs Low %TST)

N=78. Because groups differed significantly in age (High AHI/Low AHI, High %TST/Low %TST) and systolic blood pressure (High AHI/Low AHI), an analysis of covariance (ANCOVA) was performed with carotid body size as the dependent variable (left, right, average) and patient group as explanatory variables. The analysis was then adjusted for age, systolic blood pressure, diastolic blood pressure, or body mass index (BMI). The significance value for the given dependent variable is provided and corresponds to a detected difference between groups (with significance set at $p < 0.050$). Bolded values highlight significance.

	<i>AHI</i>	<i>% TST S_pO₂ 80–89%</i>
	<i>P-value</i>	<i>P-value</i>
Right Carotid Body (mm)		
Unadjusted	0.043	0.153
Age Adjusted	0.447	0.793
BMI Adjusted	0.048	0.168
SBP Adjusted	0.047	0.168
DBP Adjusted	0.049	0.169
Left Carotid Body (mm)		
Unadjusted	0.004	0.005
Age Adjusted	0.587	0.014
BMI Adjusted	0.055	0.008
SBP Adjusted	0.062	0.008
DBP Adjusted	0.049	0.007
Average Carotid Body (mm)		
Unadjusted	0.018	0.005
Age Adjusted	0.537	0.134
BMI Adjusted	0.025	0.006
SBP Adjusted	0.031	0.006
DBP Adjusted	0.022	0.005