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Research Article

Carotid body enlargement in patients with hypertension and comorbid diseases: a CT angiographic study

Karotid Cisim Boyutlarının Hipertansiyon ve Komorbid Hastalıklarla İlişkisi: BT Anjiyografik Çalışma

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Abstract

Aim: To determine the carotid body (CB) size and its relationship with hypertension, other sympathetically mediated disorders and smoking.

Materials and Methods: Neck CT angiographies of 180 patients performed in our clinic in the previous year were included in the study. The patients' histories were assessed for hypertension (HT), congestive heart failure (CHF), diabetes mellitus (DM), chronic obstructive pulmonary disease and smoking. The study groups were smokers without any chronic condition (S group, n=21), patients with HT alone (HT group, n=26), patients that had at least two chronic disorders (CD+S group, n=78) and the controls (n=33). The widest axial diameter of the CB was measured on axial sections.

Results: CB diameter could be measured in 158 patients. The CB diameter was significantly greater in HT (2.77±3.28 mm, p=0.02) and CD+S (2.76±3.38 mm, p<0.01) groups compared to the controls (2.22±3.41 mm). There was no significant difference between the S group (2.47±3.44 mm) and the control group (p=0.123). Repeated measurements showed a high intra-observer correlation for both sides.

Conclusion: HT causes a significant increase in CB size. CB size also increases significantly in individuals with the combination of sympathetically mediated disorders, including HT, CHF, and DM. CTA may provide a better understanding of the relationship between CB and sympathetically mediated diseases and guide further studies as well as therapies targeting CB.

Keywords: computed tomography angiography; carotid body; hypertension.

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Öz

Amaç: Karotid cisim (KC) boyutlarının hipertansiyon, sempatik sistem hiperaktivasyonunun görüldüğü diğer hastalıklar ve sigara ile ilişkisinin araştırılması.

Gereç ve Yöntemler: Son bir yıl içerisinde kliniğimizde boyun bilgisayarlı tomografi (BT) anjiyografi tetkiki yapılmış olan hastalar çalışmaya dahil edildi. Hastaların klinik öykülerinden hipertansiyon, konjestif kalp yetmezliği (KKY), diyabetes mellitus (DM), kronik obstrüktif akciğer hastalığı ve sigara içiciliği durumları kaydedildi. Hastalar yalnız sigara içen ve hiç komorbid hastalığı olmayan (Grup S, n=21), yalnızca hipertansiyonu olan (Grup HT, n=26), en az 2 komorbid hastalığa sahip olan (Grup KH, n=78) hastalar ve kontrol grubu (n=33) olmak üzere 4 gruba ayrıldı. BT anjiografi kesitlerinde KC'nin aksiyal planda en uzun aksı ölçüldü.

Bulgular: KC boyutu 158 hastada ölçülebildi. KC boyutu, grup HT'de (2,77±3.28 mm, p=0,02) ve grup KH'de (2,77±3,28 mm, p=0,02) kontrol grubu (2,22±3,41 mm) ile karşılaştırıldığında anlamlı olarak daha fazlaydı. Grup S (2,47±3,44 mm) ile kontrol grubu arasında anlamlı farklılık saptanmadı (p=0,123). Tekrarlanan ölçümlerde her iki taraf için yüksek gözlemci içi uyum saptandı (ICC=0,91/0,94).

Sonuçlar: Hipertansiyonu olan hastalarda KC boyutu artmaktadır. Ayrıca KC boyutu hipertansiyon, KKY ve DM gibi sempatik hiperaktivasyonun görüldüğü diğer hastalıklarda da anlamlı olarak artış göstermektedir. BT anjiyografi, KC ile sempatik hiperaktivasyonun görüldüğü hastalıklar arasındaki ilişkinin daha iyi anlaşılmasının yanında bu alandaki çalışmalarda ve tedavi seçeneklerinde yol gösterici olabilir.

Anahtar kelimeler: bilgiayarlı tomografi anjiyografi; karotid cisim; hipertansiyon

Introduction

Carotid body (CB) is the dominant peripheral chemoreceptor organ of the human body and initiates a protective chemoreceptor reflex through its sensitivity to changes in carbon dioxide, pH, potassium, and glucose in the blood (1). It has been supposed to play a role in the autonomic nervous system dysregulation and sympathetic hyperactivity, and the latter is supposed to be partially responsible for the pathogenesis of hypertension (HT), congestive heart failure (CHF), and diabetes mellitus (DM) (2-7). It has been suggested that resection of CB and blockade of P2X3 receptors in CB can be used in the treatment of hypertension (8,9).

Computed tomographic angiography (CTA) and ultrasonography studies have shown that CB can be visualized on routine examinations and that increased CB size is associated with HT, CHF, and DM (10-13). However, to the best of our knowledge, the isolated effect of smoking on CB size has never been demonstrated in detail. Therefore, this study aimed to determine the CB dimensions and its correlations with smoking, HT, and other disorders associated with sympathetic hyperactivity.

Material and Methods

Our hospital's electronic patient recording system was used to extract the data of the patients who had neck CTA. The patients diagnosed with HT, DM, CHF, and/or chronic obstructive pulmonary disease (COPD) for at least three years were included in the study. Smoking status and the demographic characteristics of the patients were also recorded from the hospital's electronic patient recording system. The local ethics committee has approved the study protocol of this retrospective study and written informed consent was obtainede from all patients.

The neck CTA scans performed in our institution in the previous year before starting the study were analyzed retrospectively, and a total of 180 patients who underwent neck CTA were found. Five patients with inadequate arterial phase, 12 patients with motion artifacts were excluded, and 163 patients' CTA scans were examined. After examination, the patients with CB borders were indistinguishable from the adjacent vascular structures on both sides, and the patients with carotid stents were also excluded to avoid measurement errors.

CB could not be visualized on the right side in 8 (4.9%) and on the left side in 11 (6.7%) patients. CB could not be distinguished on either side in 2 (1.2%) patients. The visualization rate was 93.8% on the left (153 of 163 patients) and 92% on the right (150 of 163 patients). Unilaterally visualized and measured CBs were included in the statistical analysis. The total number of patients included in the study was 158.

The criteria for exclusion and the numbers and rates of the included and excluded patients are presented in the flowchart of patient selection (Figure 1).

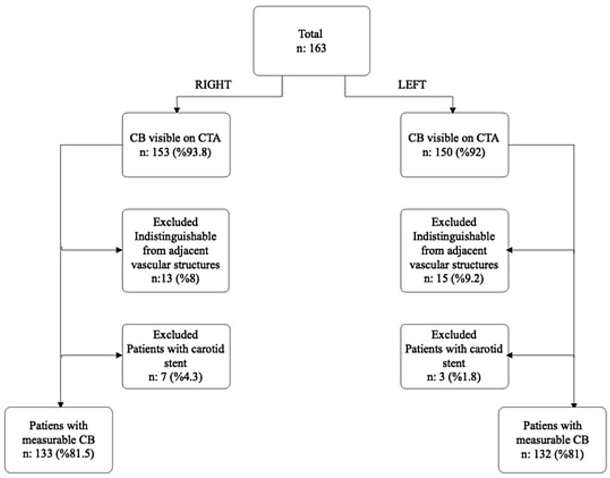

Figure 1. The flowchart of patient selection.

Study groups

The control group consisted of non-smokers without any of the chronic disorders investigated (n=33).

The study group was divided into three subgroups as:

1. Smokers only (S group) (n=21),

2. The patients with hypertension alone (HT group) (n=26),

3. The patients with at least two chronic disorders or the smokers with one chronic disorder (CD+S group) (n=78). This group included 71 patients with hypertension, 33 with diabetes mellitus (DM), 13 with chronic heart failure (CHF), and 13 with chronic obstructive pulmonary disease (COPD). In this group, 52 individuals were smokers.

Imaging protocol

The CTA scans were obtained with a 64 multi-row detector CT system (Aquilion 64, Toshiba Medical Systems, 2011, Japan). The CT protocol parameters were as follows: Tube voltage: 120 kV, tube current: 300 mA, rotation time: 0.5 sec, pitch: 0.6, axial section thickness: 0.5 mm, reconstruction interval: 0.4 mm. The scans were performed between the inferior border of the aortic arch and the superior border of the frontal sinus. The bolus tracking method was used for contrast delay, and the imaging was started when the aortic density was 120 Hounsfield units (HU). 100 ml non-ionic, iodinated contrast agent (350 mg/ml iodine concentration) and then 30 ml saline were administered intravenously from the antecubital vein through an 18-20 G catheter at a rate of 5 ml/sec, using an automatic pump (Ulrich Medizin technical version, 2004, Germany).

Image Analysis

The obtained CTA images were examined on axial, sagittal, coronal or oblique plans in the work-station using Aquarius iNtuition® software (ver. 4.4.11.82.6784, California, USA). To obtain a standard view, 200% magnification was used at a window width of 700 and a window level of 200. The usual CB localization, the infero-medial aspect of the carotid bifurcation, was examined to identify CB. In the aforementioned localization and on the axial sections, the ovoid structure, which was highly enhanced in the arterial phase, was considered CB (Figure 2). Axial, coronal, sagittal, coronal oblique and sagittal oblique images were examined in terms of the location, size, and borders of CB (Figures 3, 4).

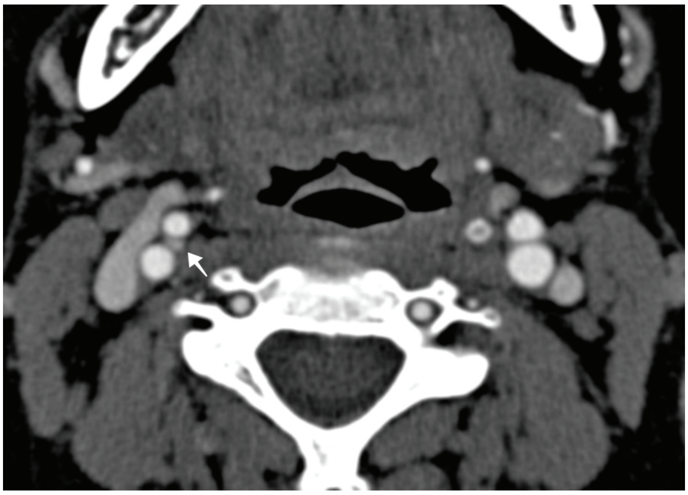

Figure 2. Axial CT image. Normal CB (arrow) in the right carotid bifurcation.

Figure 3: Sagittal MIP image. Normal CB (arrow) in the right carotid bifurcation.

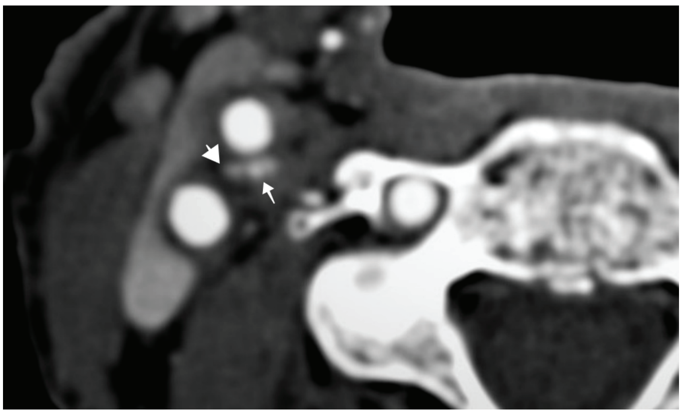

Figure 4. Axial CT image. CB in the right carotid bifurcation (arrow) and a branch of external carotid artery adjacent to CB (arrowhead).

The images with motion artifacts or with an inadequate arterial phase, the patients with CB tumors, tubular structures suggestive of vessels showing continuity in the consecutive sections, and the CB-like structures which were not located in the typical site were excluded. To avoid measurement errors, the CBs were excluded if their borders could not be clearly distinguished from the neighboring vessels (Figure 5). The sides on which patients had carotid stents were excluded since the borders of CB could not be distinguished clearly due to streak artifacts.

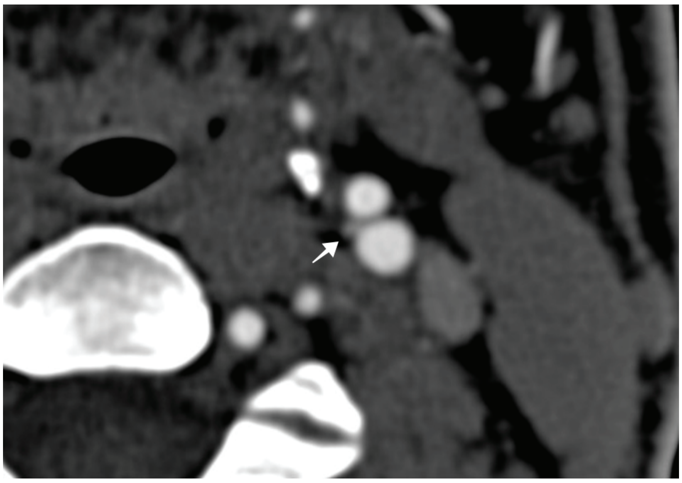

Figure 5. Axial CT image. CB in the left carotid bifurcation with indistinguishable borders from internal and external carotid arteries (arrow).

Since no standard technique has yet been determined to measure the CB size, and coronal, sagittal, and oblique sections have spatial resolution limitations, the CB diameters were measured only on axial sections. The measurements were performed by a single radiologist with 5-year experience and blinded to patient data. On axial sections where CB was seen the largest on both sides, the longest axis of CB was measured (Figure 6).

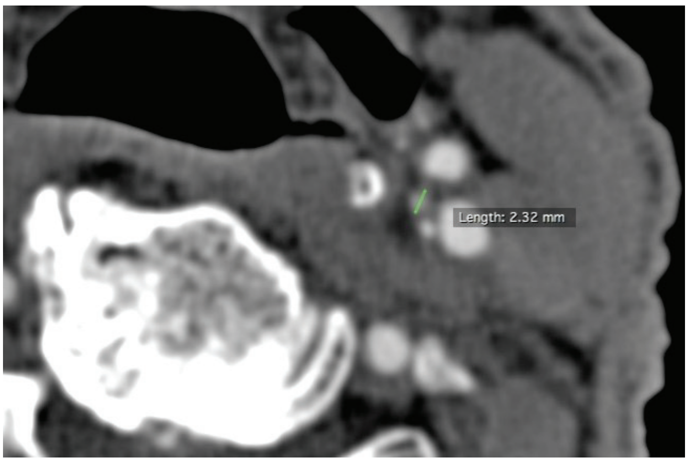

Figure 6. Measurement of CB's longest diameter on axial CT image.

Thirty patients were selected randomly without any distinction among the study groups, and the measurements were repeated independently of the initial measurements to test intra-observer agreement.

Statistical analysis

The data were analyzed using SPSS v.15.0 (SPSS Inc., Chicago, USA) package program. The descriptive statistics were presented as mean and standard deviation for the variables with normal distributions and median and minimum-maximum values without normal distribution. The numbers and percentages were presented for nominal variables. Two-group comparisons of the means were analyzed with Student's t-test, and two-group comparisons of the medians were analyzed with the Mann-Whitney U test. Kruskal Wallis test was used to analyze the difference of medians when the number of groups was more than two. Bonferroni correction was performed to determine the group causing the difference. Nominal variables were analyzed with Pearson Chi-Square or Fisher exact tests. Generalized Estimating Equations (GEE) analysis was used to test whether the right and left CB measurements affected the study group, age, or gender factors. The Wilcoxon test compared right and left CB measurements on the axial plane since the group distributions were not normal. Intraclass Correlation Coefficient (ICC) was used to analyze the intra-observer agreement. $P < 0.05$ was considered as statistically significant.

Results

The ages of the control and S groups were similar (p=0.129); however, the mean ages of the HT and CD+S groups were significantly higher than the control group (p=0.001 for both). The gender distribution was homogenous in the control and HT groups (p=0.218 and p=0.175, respectively); however, it was heterogeneous in the S group and the CD+S group (p=0.004 and p=0.015, respectively). The male/female ratio was higher in the S group and the CD+S group. The demographic data of the study groups are summarized in Table 1.

Table 1. Demographic characteristics of the study groups.

	Gender					
	Female	Male	Total (n)	Age (years) Median (min-max)	p for age	p for gender
Control	19 (58%)	14 (42%)	33	49 (18-88)	-	0.218
S	6 (%29%)	15 (71%)	21	48 (21-68)	0.129	0.004§
HT	18 (69%)	8 (31%)	26	65 (50-67)	0.001*	0.175
CD+S	31 (40%)	47 (60%)	78	63 (25-88)	0.001*	0.015§
Total (n)	74 (47%)	84 (53%)	158			

S: Smoking group, HT: Hypertension group, CD+S: Chronic disorder + smoking group. * The median ages of HT and CD+S groups are greater than the S group and the control group. § The gender distribution is not homogenous in S group and CD+S group.

The mean diameters of CB were 2.62 ±0.7 mm and 2.62 ±0.76 mm on the right and left sides, respectively, without any statistically significant difference between them (p=0.167). The CB diameter was not significantly correlated with age (Pearson's r=0.218; p=0.078) or gender (p=0.289).

Considering age and gender, the right and left CB diameters were analyzed altogether and compared with GEE analysis. There was no significant difference between the control group and the S group for CB diameters (p=0.123), however HT group (p=0.020) and CD+S group (p= 0.001) had greater CB diameters compared to the control group (Table 2).

Table 2. Comparison of CB diameters among the study groups.

Groups	Mean	Standard Deviation	95% Wald Confidence interval		P
			Lower	Upper	
Control	2.22	3.41	-4.47	8.92	-
S Group	2.47	3.44	-4.28	9.23	0.123
HT Group	2.77	3.28	-3.68	9.2	0.020*
CD+S Group	2.76	3.38	-3.86	9.4	0.001*

*p<0.05
S: Smoking group, HT: Hypertension group, CD+S: Chronic disorder + smoking group.

Thirty patients were randomly selected without taking the study groups into consideration, and the observer performed two measurements at different times to evaluate intra-observer repeatability and agreement. Intraclass Correlation Coefficient (ICC) was found as 0.91 on the right and 0.94 on the left side, which indicated a strongly high intra-observer agreement.

Discussion

In this study, we found that smokers without any comorbid disease did not have a higher CB diameter compared to the controls. A greater CB diameter was determined in patients with HT alone and those with at least two sympathetically mediated chronic conditions compared to the controls.

The small size of CB and the difficulty of its dissection have made studies on CB difficult. Until recently, our knowledge about CB was limited to animal experiments and postmortem studies, but it is now possible to visualize CB in vivo by means of different imaging modalities (10-13). Normal CB has a high vascularity and this feature allows its detection on CTA images. Nguyen et al. were the first authors who demonstrated normal CB on routine neck CTA studies in 2011 (10). In our study, CB was seen on the right in 93.8% of the patients who underwent CTA, and on the left in 92%, which was higher than the rates reported in the literature (10-12). This result may be explained by thinner section thickness, 0.5 mm, we used in the axial reconstructions; the cross-section thickness of 1 mm was used in the aforementioned studies.

The normal-sized CB should be differentiated from nerve sheath or CB tumors; therefore the normal radiological limits of CB diameters should be determined. CB tumors can be easily identified in cross-sectional imaging modalities since they reveal typical findings when they are bigger than certain diameters. However, the absence of typical imaging findings in tumors smaller than 10 mm in diameter makes the differential diagnosis difficult in lesions located in this region (14). In our study, the maximum CB diameter was 3.5 mm in patients with no comorbid disorders and 6.8 mm in patients with a sympathetically mediated comorbid disease. In light of this data, a highly contrast-enhanced structure measured less than 7 mm in its maximum diameter on transverse plain should be considered normal CB, provided that they are in their typical localization.

The relationship between CB hypertrophy and the disorders with sympathetic hyperactivity, including HT, CHF, and DM, has been demonstrated in several studies (11,12,15). Cramer et al. showed that the patients with at least one of HT, CHF, or DM had a 20-25% increase in CB size compared to the control group (11). Nair et al. found a significant increase in CB diameter in patients with HT and CHF compared to the control group (12). In addition to these studies, greater CB diameters were found in the patients with HT alone (16). Similarly, we found a significantly greater CB diameter in patients with HT alone, and in patients with more than one sympathetically mediated disease.

It has been known that high altitude and chronic hypoxia-related states play a role in the etiology of CB tumors (17,18). It may be assumed that chronic hypoxia may affect the CB size, and cause hypertrophy. Smoking may cause chronic hypoxia, and thus may cause an increase in the size of CB. Although Nguyen et al. reported that smoking was not correlated with CB hypertrophy, they did not provide statistical data, and to the best of our knowledge, no studies in the literature have investigated the isolated effect of smoking on CB diameters on CTA in detail after excluding other conditions with sympathetic hyperactivity (10). In our study, we found that smokers without any sympathetically mediated disorders did not have increased CB diameters (p=0.123). This may be explained by the absence of chronic hypoxemia in smokers without chronic lung disease.

After CB's role in disorders with sympathetic hyperactivity has been revealed, treatment options targeting CB have come to the agenda. In preclinical experiments, CB denervation in rats with spontaneous HT has been shown to cause a decrease in systemic blood pressure (2,19). Recently, human studies of CB resection in the treatment of essential HT and CHF reported promising results (20-24). We think that the evaluation of CB location and size with CTA may be useful for the research and development of treatment options targeting CB.

Our study has some limitations. First, when evaluating CB hypertrophy, volume measurement would give better results due to the irregular and asymmetrical shape of the organ. However, the volume measurements made on the workstations on CTA images do not provide reliable results due to the small size of CB. In our study, the longest axial diameter was measured to evaluate the CB dimensions, and the single-axis measurement was insufficient to measure the volume of this organ. Also, although we found statistically significantly different CB sizes in our study groups, the difference was approximately 0.5 mm due to the small size of CB. There were overlaps in the CB diameters among the study groups. This makes a determination of a definitive cut-off value difficult when evaluating the increase in CB diameters. Second, although we planned to investigate the relationship of CB diameters with DM, CHF, and COPD separately at the beginning of our study, we could not do this due to the small number of patients with the aforementioned disorders; therefore, we included all those disorders into CD+S group. The retrospective nature of our study did not let us consider the severity of these conditions, whether the patients were on treatment or not, as well as the determination of the duration of the disorders and hence their correlations with CB size.

Conclusion

It is possible to visualize normal CB on CTA in the majority of cases. Smoking, in absence of any sympathetically mediated disorder, does not cause a significant increase in CB size. In hypertensive individuals, there is a greater CB size, independent of other sympathetically mediated disorders. CB size also increases significantly in individuals with combination of disorders related to sympathetic hyperactivity such as HT, CHF, and DM. CTA may provide a better understanding of the relationship between CB and sympathetically mediated disorders and guide further studies as well as therapies targeting CB.

Declerations

Ethical approval

Our retrospective study has been approved by the local ethics committee (E-15-590).

Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article.

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