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ORIGINAL RESEARCH

Evaluation of Carotid Artery Intima Media Elasticity in Takayasu Arteritis by Shear Wave Elastography*

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ABSTRACT

This study aimed to evaluate carotid morphology with Ultrasound (US) and arterial stiffness with Shear Wave Elastography (SWE) in TA patients and to compare results with disease activity. We searched the clinical archive and found 41 Takayasu Arteritis (TA) patients with carotid involvement had carotid US and SWE screening. Patients (n=22) with confounding factors that could affect the carotid wall were excluded. Nineteen cases that meet the inclusion criteria and 19 healthy control cases age-sex matched were compared. We evaluated right and left common carotid artery intima-media thickness (IMT) with B-Mode US and wall stiffness with SWE. We also investigated a relationship between disease activation and arterial stiffness. Carotid artery IMT was significantly higher in TA than in the control group ($p<0.001$). Median stiffness values for the carotid wall in TA were 28.3 kPa and 36.3 kPa on the right and left and in the control group 26.1 kPa and 28.1 kPa, respectively. The left CCA stiffness was significantly higher in the TA than in the control group ($p=0.03$), whereas the difference in right CCA elasticity did not reach statistical significance. A left CCA cut-off value of 52 kPa reached the highest accuracy with a specificity of 100% and a sensitivity of 36.8% in TA. No significant relationship was found between disease activation and elasticity value. SWE alone is not diagnostic but can be a useful adjunctive modality to gray-scale ultrasound in assessing carotid artery involvement with TA.

Keywords: Takayasu Arteritis. Ultrasound. Shear Wave Elastography. Carotid Stiffness. İntima Media Thickness.

Takayasu Arteritinde Karotis İntima Media Elastikiyetinin SWE ile Değerlendirilmesi

ÖZET

Bu çalışmanın amacı Takayasu Arteriti (TA) hastalarında Ultrasonografi (US) ile karotis morfolojisini ve Shear Wave Elastografi (SWE) ile arteriyel sertliği değerlendirmek ve sonuçları hastalık aktivitesi ile karşılaştırmaktır. Klinik arşiv taranmış ve karotis tutulumu olan, karotis US ve SWE görüntülemesi yapılmış 41 TA hastası bulundu. Karotis duvarını etkileyebilecek kafa karıştırıcı faktörleri olan hastalar (n:22) çalışma dışı bırakıldı. Dahil edilme kriterlerini karşılayan 19 hasta ve yaş ve cinsiyet açısından benzer 19 sağlıklı kontrol olgusu karşılaştırıldı. B-Mode US ile sağ ve sol ana karotis arter intima-media kalınlığı (IMT) ve SWE ile duvar sertliği değerlendirildi. Ayrıca hastalık aktivasyonu ile arteriyel sertlik arasındaki ilişki de araştırıldı. Karotis arter İMK, TA'da kontrol grubuna kıyasla anlamlı derecede yüksek bulundu ($p<0,001$). Karotis duvarı için medyan sertlik değerleri TA'da sağ ve solda sırasıyla 28,3 kPa ve 36,3 kPa, kontrol grubunda ise 26,1 kPa ve 28,1 kPa idi. Sol CCA sertliği TA'da kontrol grubuna kıyasla anlamlı derecede yüksekken ($p=0,03$), sağ CCA sertliğinde anlamlı farklılık saptanmadı. TA'da 52 kPa'lık sol CCA cut-off değeri %100 özgüllük ve %36,8 duyarlılık ile en yüksek doğruluğa ulaşmıştır. Hastalık aktivasyonu ile elastikiyet değeri arasında anlamlı bir ilişki bulunmadı. SWE tek başına tanısal değildir, ancak karotis tutulumunu değerlendirmede B-Mode US'ye ek olarak yararlı bir yöntem olabilir.

Anahtar Kelimeler: Takayasu Arteriti. Ultrason. Shear Wave Elastography. Karotis Sertliği. İntima Media Kalınlığı.

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Takayasu Arteritis (TA) is a chronic inflammatory vasculitis affecting large vessels like the aorta and its major branches, pulmonary artery, coronary and renal arteries[1,2]. It is mainly seen in young adult females, and the subclavian artery is the most commonly affected vessel (common on the left side), followed in order by the aorta, the common carotid artery (common on the left side), renal, vertebral, and innominate arteries[3]. Infection, autoimmune, and genetic factors may play a role in pathogenesis, though the exact etiology is not clear[4]. The disease progresses with activation and remission. There are several classifications for assessing disease activation. The Indian Takayasu Clinical Activity Score (ITAS2010) is the main current attempt to develop a disease activity score for TA[5]. ITAS2010 assesses the clinical features of a newly emerging disease in the previous 3 months, as assessed by the physician[5].

Since clinical and laboratory findings are unreliable in diagnosis, imaging techniques have a crucial role. Digital Subtraction Angiography (DSA) is the gold standard imaging modality. However, the invasive nature, relative complication rate, and radiation exposure are the main disadvantages[6]. Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA) are alternative imaging modalities that can demonstrate vascular stenosis, occlusions, and aneurysms, and are effectively used for differential diagnosis and follow-ups[7]. Recently, (18F) fluorodeoxyglucose positron emission tomography (18F-FDG-PET) has a higher sensitivity for early diagnosis and evaluation of response to treatment and is also recommended compared to other conventional methods[8,9]. Ultrasonography avoids the high radiation dose of angiography and 18-FDG-PET and is cheaper and more widely available, especially in less- resourced countries where TA is more common[10]. It can assess the vessel wall thickening, morphology, thrombosis, and aneurysm formation, especially for carotid arteries[11]. Shear Wave Elastography (SWE) is an ultrasound-based imaging modality that can measure tissue stiffness based on acoustic radiation force excitations. On SWE, color elastogram maps can be imposed on B-mode grayscale images simultaneously, allowing the acquisition of anatomic and tissue elasticity data[12,13]. Given the inflammatory nature of changes in Takayasu Arteritis, there might be changes in tissue stiffness along the affected vessel walls, which may precede increased IMT.

This study, assessed the intima-media thickness of common carotid arteritis by B-Mode Ultrasonography and arterial stiffness by SWE in patients with Takayasu Arteritis. Also, we investigated the relationship between arterial stiffness and clinical activation of the disease. We hypothesized an increase in vessel wall stiffness due to the involvement of inflammatory vascular diseases.

Material and Method

The study was performed in line with the principles of the Declaration of Helsinki, and the Local Ethics Committee approved the study protocol (approval number 2011-KAEK-26). A retrospective review of the clinical archive identified 41 cases consistent with Takayasu Arteritis based on clinical, laboratory, and radiological data. Patients with confirmed carotid artery involvement based on CTA, MRA, or DSA and who had performed carotid ultrasound and SWE were included in the study. To minimize confounding factors that could affect the carotid artery wall, 16 patients with a smoking history or comorbidities like diabetes mellitus, atherosclerotic disease (etc. cerebrovascular disease, myocardial infarction), hyperlipidemia, and radiation were excluded. Thus, we only evaluated the effect of Takayasu Arteritis on the vessel wall. Six patients who performed B-mode ultrasound but not SWE were excluded. 19 cases that meet the inclusion criteria were identified. Nineteen age- and sex-matched cases that performed a carotid ultrasound and SWE for vascular pathologies and were completely normal constituted the control group. All individuals' ages and gender were recorded. Clinical examination findings 3 months before and after ultrasound were recorded for disease activation according to the ITAS2010[5] classification of all patients. It was investigated whether there was a relationship between carotid elasticity values and disease activation.

Ultrasound protocol

All ultrasound examinations were performed by a single radiologist (with 11 years of experience in ultrasound and 3 years of experience in SWE) using Aplio i600 (Canon Medical System, Tokyo, Japan) equipped with a high frequency (4-11 MHz) linear transducer. During the examination, patients were in a supine position with their heads in slight extension. Bilateral common carotid arteries (CCA) were assessed in gray-scale mode in axial and longitudinal planes. The hyperechoic line of the intima-media layer was evaluated, and intima-media thickness was measured at the mid-level of CCA from the posterior wall using the automatic edge detection feature (Figure 1). SWE measurements were performed from the anterior CCA wall during the diastolic phase. The time when the vessel diameter reached its maximum was considered as the diastolic phase of the heart. For SWE, a q-box (quantitative box) was placed manually on the intima-media layer of the carotid wall. Subsequently, a rectangular region of interest (ROI) was semi-automatically drawn

(Figure 2). During ROI placement, attention was paid to excluding the vessel lumen and neighboring soft tissue in the ROI. Three consecutive measurements were performed for each CCA, and the mean value was used for statistical analysis. All SWE measurements were recorded as shear wave velocities using m/s and kPa as units in our local picture archiving and communication system.

Figure 1.
A 21-year-old female patient with Takayasu Arteritis. Representative image for measurement of right common carotid artery intima-media thickness.

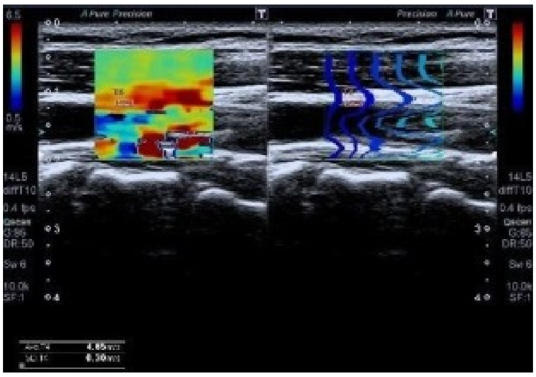

Figure 2.
A 42-year-old female patient with Takayasu Arteritis. Demonstrative case for shear wave elastography measurement. Elastography measurements were performed based on color maps (left). The image on the right demonstrates the propagation waves caused by artifact in the arterial wall.

Statistical Analysis

A Shapiro–Wilk test was used to assess the normal distribution of the variables. Group comparisons were performed with independent t, Mann Whitney U, or Wilcoxon Signed Rank tests. Descriptive statistics were presented as mean ± standard deviation and median (minimum - maximum) value. Receiver operator characteristic (ROC) analysis was used to determine the cut- off value for left CCA stiffness. SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and MedCalc Statistical Software trial version (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2016) were used for statistical analysis. The level of statistical significance was taken as $\alpha = 0.05$.

Results

A total of 38 cases; 19 cases confirmed diagnosis of TA with arterial involvement, and 19 control cases were included. All TA and control group cases were female. Mean ages were 38.7 and 40 years for the control group and TA, respectively. No statistically significant difference was observed (p=0.62). The mean follow-up period of TA patients from diagnosis was 60 months (3- 168 months).

In B-Mode Ultrasound, carotid artery intima-media thickness (IMT) was significantly higher in TA (median right CCA IMT: 1.1 mm, left CCA IMT: 0.9 mm) than in the control group (median right CCA IMT: 0.5 mm, left CCA IMT: 0.5 mm) (p<0.001). The hyperechoic line of the intima-media layer was irregular in all TA patients and had a regular morphology in the control group. There was no plaque formation in the CCA in TA and healthy group. Findings range from mild luminal narrowing to total occlusion in the CCA due to increased IMT in TA patients. Seven (37%) patients have bilateral normal lumen width, 7 (37%) patients have bilateral and 2 (10,5%) unilateral slightly narrowed due to IMT increase, 2 (10,5%) patients have unilateral severe occlusion, and 1 (5%) patient has unilateral total occlusion in the CCA.

In SWE, the median arterial stiffness for the CCA wall in Takayasu Arteritis was 28.3 kPa and 36.3 kPa on the right and left, respectively. In contrast, median arterial stiffness for CCA wall in the control group were 26.1 kPa and 28,1 kPa on the right and left, respectively. The difference for the right CCA stiffness values did not reach statistical significance (p=0.402). The left CCA stiffness values were significantly higher in Takayasu Arteritis compared to the control group (p=0.03) (Table I).

Table I. Carotid elasticity values in Takayasu arteritis and healthy control group

	Control Group (n:19)	Takayasu Arteritis (n:19)	p
Right CCA Elasticity (kPa)	26.1 (13-49)*	28.3 (11.5-97.3)*	0.402
Left CCA Elasticity (kPa)	30.5 (15.2-52.3)*	36.3 (13.3-115.6)*	**0.030**

*data is presented as median (minimum-maximum), n: number of patient

When left and right CCA stiffness values were compared among Takayasu Arteritis cases, left CCA stiffness values were significantly higher than right CCA (p=0.004). In the control group, there was no significant difference between the left and right CCA stiffness values (p=0.099).

ROC analysis was performed separately for the left and right sides to determine the best cut-off value to differentiate between arteritis cases and the control group. There was no statistically significant cut-off value for the right side (area under curve=0.582, p=0.408). The cut-off value was 52 kPa for the left side (area under curve=0.706, p=0.017) (Table II, Figure 3a- 3b). This cut-off value achieved a specificity of 100% and a sensitivity of 36.8%.

Table II. AUC table for common carotid artery elasticitiy values

	Cut-off value	Sensitivity	Specificity	Youden J	AUC	p
Right CCA	-	-	-	-	0.582	0.409
Left CCA	>52.3	36,8%	100%	0.3684	0.706	**0.017**

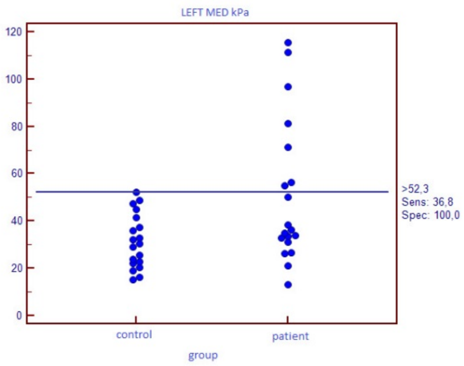

Figure 3a.
A desirable cut-off value for left CCA ratios and dot graphic

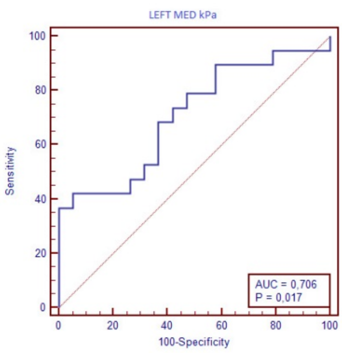

Figure 3b.
ROC curve based on left CCA shear wave elastography values. The area under the curve was 0.706. The cut-off value of 52 kPa achieved a specificity of 100% and sensitivity of 36.8%.

According to ITAS2010 criteria, 5 patients were in the active stage of the disease, and 14 patients were inactive. The right carotid stiffness median value was 28 kPa, and for the left side, it was 36,3 kPa in the activation stage in patients. The median value of the right carotid stiffness was 30.3 kPa, and for the left side it was 36.6 kPa in the inactive stage in patients. These results showed no significant difference between the active and inactive patients' right and left carotid stiffness values (p=0,622, p=0,823). However, there was a statistically significant relationship between the right and left values in the active patient group (r=0,975, p=0,005) and the inactive group (r=0,758, p=0,002); there was a higher correlation in the active group than in the inactive group.

Discussion and Conclusion

Takayasu Arteritis is an inflammatory large-vessel vasculitis involving three layers of the arterial wall, characterized by diffusely increased intima-media thickness, irregularity of the hyperechoic lines, and decreased lumen caliber on ultrasound[1,14]. Carotid ultrasound in healthy individuals shows normal intima-and media layer as two hyperechoic uniform lines[14]. In this study, we have identified increased IMT and irregularity of the hyperechoic lines in bilateral CCAs of Takayasu Arteritis compared to healthy controls in B-Mode ultrasound, which aligns with the available literature[14-16].

Numerous prior studies in the literature showed SWE's role in assessing carotid artery wall stiffness in different conditions like cardiovascular disease, carotid plaques, and aging[17-20]. Very few studies evaluate cervical arteries in inflammatory vascular diseases with SWE[21,22.] It has been reported that CCA stiffness increases in these diseases as well. To the best of our knowledge, this is the first study in literature about this topic. In our study, we performed carotid ultrasound and SWE in carotid artery involvement with TA. Although bilateral carotid intima- media thickness increased, there was no significant difference in right CCA stiffness between the TA and control groups; we found that the left CCA stiffness was significantly higher in the TA group than in the control group. A literature review shows a higher left subclavian and common carotid artery involvement rate in TA[23,24]. However, there is no definitive reason for this situation. This might be related to the direct origin of CCA from the aortic arch on the left and the brachiocephalic artery on the right. The left CCA might be exposed to greater hemodynamic changes due to its direct origin, which can account for a higher predilection for the left side. Also, when we evaluated the left and right sides separately to determine the best cut-off value to differentiate between TA and the control group, a cut-off value of 52 kPa achieved a specificity of 100% for the left CCA arteritis. Left CCA stiffness values of all patients were above 52 kPa. There is no cut-off value defined in the literature. Our study and cut-off value may be a guide for future studies. Therefore, this is a noteworthy finding as SWE may be used as an additional modality of overt intima-media thickness in patients with presumptive carotid involvement in TA. Additional assessment of the carotid wall using SWE in cases of TA can increase the accuracy of ultrasound assessment. In cases with normal intima-media thickness and elasticity below the cut-off value, arteritis can be excluded more accurately in the imaged vessel segment. SWE has potential advantages as it can be simultaneously acquired during gray-scale ultrasound. It is also more reproducible compared to other ultrasound elastography techniques. However, using SWE as a routine may not be effective, since the sensitivity values are low (sensitivity: %36,8).

Some difficulties may be experienced in evaluating activation in TA because the inflammatory activity in the vessel wall and the systemic inflammatory response do not always show a positive correlation[25]. Monitoring of disease activity in TA can be accomplished with the integrated use of non-invasive imaging methods, patient symptoms, clinical findings, and acute phase reactants[26]. However, no single imaging method can provide all the necessary information, and each method has different and complementary roles in monitoring[27]. Due to its high resolution, the US is particularly promising in imaging the carotid artery wall and detecting millimetric increases in wall thickness[28,29]. In addition to these data, our study evaluated vessel wall elasticity in terms of activation with SWE. Considering the elasticity values obtained with SWE, there is no significant relationship between disease activation and elasticity values. It also does not provide additional information in terms of disease activation. This result may be due to the small number of patients.

There are some limitations in our study. Our study was retrospective, and patients did not have regular intervals for ultrasound controls. The patient population was heterogeneous, including recently diagnosed treatment naïve cases and medically managed cases imaged during follow-up, because the study was cross-sectional. Relatively low patient numbers limited our study due to exclusion criteria. Future studies with larger patient populations with greater statistical data could overcome this limitation.

In conclusion, we evaluated the carotid wall stiffness of TA patients for the first time using SWE. SWE alone is not diagnostic, but it can be a potentially useful adjunctive modality to gray-scale ultrasound in assessing common carotid artery involvement in patients with Takayasu Arteritis. The cut-off value we stated is valuable for the literature and should be evaluated with other studies.

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Approving Committee: Bursa Uludag University Faculty of Medicine Clinical Research Ethics Committee
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Idea and design: B.E.G., S.G.K.; Data collection and processing: B.E.G., B.Y., Y.P.; Analysis and interpretation of data: B.E.G., İ.E., N.B.T.; Writing of significant parts of the article: B.E.G.
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