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ARAŞTIRMA / RESEARCH

Relationship between the Achilles tendon strain ratio and the presence of mitral annulus calcification

Aşil tendonu gerinim oranı ile mitral anulus kalsifikasyonu varlığı arasındaki ilişki

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Abstract

Purpose: We aimed to investigate the significance of Achilles tendon (AT) thickness (T) and AT strain ratio (SR), determined by AT ultrasonography (US) and strain elastography (SE), in determining patients with mitral annulus calcification (MAC).

Materials and Methods: 100 patients (65 females, 35 males, mean age 64.7 ± 12.1 years) diagnosed with MAC after echocardiography and 50 control subjects (32 females, 18 males, mean age 63.2 ± 12.8 years) with similar cardiovascular risk factors were included. Laboratory tests and AT US were performed. AT T and AT-SR were calculated.

Results: AT -T and AT-SR were found to be significantly higher in patients with MAC. In multivariate logistic regression analysis, AT -T and AT-SR independently determined the risk for MAC. According to this analysis, AT -T (1 mm each) and AT-SR (0.1 each) increased the risk for MAC by 69.9% and 12.7%, respectively. When ROC was analyzed using AT -T and AT-SR to predict patients with MAC, the areas under the curve (AUC) of ROC were 0.684 and 0.819, respectively. In the same analysis accepting the cut-off value of 1.25 for AT-SR, the presence of MAC was detected with a sensitivity of 94.1% and a specificity of 76.2%.

Conclusion: AT-SR detected in AT SE examination is a simple, reproducible, inexpensive, and noninvasive parameter that can be used to predict patients with MAC. This may be due to the fact that the increase in MAC and AT-SR may be associated with similar physiopathological mechanisms.

Keywords:. Achilles tendon strain ratio, mitral annulus calcification, Achilles tendon thickness, strain elastography.

Öz

Amaç: Aşil tendonu (AT)- ultrasonografisi (US) ve gerinim elastografisi (SE) ile elde edilen AT- kalınlığı (T) ve AT- gerinim oranının (SR) mitral kapak kalsifikasyonlu (MAC) hastaları belirlemedeki önemini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya ekokardiyografi sonrası MAC tanısı alan 100 hasta (65 kadın, 35 erkek ve ortalama yaş 64.7 ± 12.1) ve kardiyovasküler risk faktörü benzer olan 50 kontrol (32 kadın, 18 erkek ve ortalama yaş 63.2 ± 12.8) alındı. Laboratuvar incelemeler ve AT US yapıldı. AT-T ve AT-SR hesaplandı.

Bulgular: MAC olan hastalarda AT-T ve AT-SR belirgin olarak yüksek olduğu bulundu. Logistic regresyon analizinde, AT-T ve AT-SR değerlerinin MAC olma riskini bağımsız olarak belirlediği bulundu. Bu analize göre AT-T (her 1 mm) ve AT-SR (her 0.1)'nin MAC olma riskini sırası ile %69.9 ve %12.7 oranlarında artırdığı saptandı. AT-T ve AT-SR değerlerinin MAC olan hastaları belirlemesi açısından ROC analizi yapıldığında, ROC eğri altında kalan alanın sırası ile 0.684 ve 0.819 belirlendi. Aynı analizde, AT-SR için sınır değer 1.25 olarak alındığında %94.1 sensitivite ve %76.2 spesivite ile MAC varlığını belirlediği tespit edildi.

Sonuç: AT SE incelemesinde saptanan AT-SR, MAC olan hastaları önceden belirlemede kullanılabilecek basit, ucuz, tekrarlanabilir ve non-invaziv bir parametredir. Bu durum MAC ve AT-SR artışının benzer fizyopatolojik mekanizma ile meydana gelebilmesinin bir sonucu olabilir.

Anahtar kelimeler: Aşil tendon gerinim oranı, mitral anulus kalsifikasyonu, Aşil tendon kalınlığı, gerinim elastografisi.

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INTRODUCTION

Mitral annular calcification (MAC) occurs when the fibrous structure of the mitral valve chronically degenerates and calcifies with age. The prevalence increases with age, concomitant cardiovascular disease, and the presence of renal disease and ranges from 8-15%[1-5]. MAC is usually an incidental finding in patients being evaluated for cardiovascular or pulmonary disease and is associated with cardiovascular risk factors. Patients with MAC have a higher prevalence of atrioventricular block, bundle branch block, intraventricular conduction delay, and atrial fibrillation[1-5]. Although the presence of MAC can be detected with direct chest radiography, the most ideal diagnostic method is echocardiography[6,7]. MAC can be effectively and noninvasively diagnosed with multislice computed tomography (CT) and electron beam examination CT[2]. However, the CT examination is not performed specifically to diagnose MAC but can be diagnosed as a concomitant disease during examination of the heart, aorta, and coronary arteries CT.

The Achilles tendon (AT) is the largest, strongest, and thickest tendon in the human body[8]. AT is most commonly examined in clinical practice because of trauma and most commonly with magnetic resonance imaging (MRI) and ultrasonography (US). Examination of the Achilles tendon is also recommended in the diagnosis and follow-up of patients with familial hyperlipidemia (FHL)[9-11]. US elastography or sonoelastography is a new ultrasound examination and provides important information about the elastic properties and tissue stiffness of various lesions and tissues.

Strain elastography (SE) is a method of sonoelastography in which the measurement is made by a ratio between the hardness of the tissue under examination and the reference tissue. As tissue stiffness increases, the strain ratio increases, and the strain ratio is measured as high for malignant lesions and hard tissues. This new technique has been used to evaluate many tissues such as breast and thyroid tissue/lesions. Recently, it has also been used to evaluate AT[12-16].

The literature review shows that SE is most commonly used to differentiate between benign and malignant lesions, especially in superficial organs and superficial tissues such as breast and thyroid. AT elastography, on the other hand, has been studied mainly in patients with familial hypercholesterolemia, and the relationship between it and its usefulness in follow-up has been investigated[9-11]. There are also studies investigating the relationship between age, obesity, smoking, and AT elastography characteristics[13-15]. There is also an AT elastography study investigating the change in AT stiffness in patients with diabetic foot[16].

It has been clearly shown that there is an increase in AT thickness (AT -T) and AT strain ratio (AT-SR) in the presence of CAD risk factors, especially in the presence of CAD, age and hyperlipidemia[9,10,13-15,17-20]. The presence of MAC is closely associated with cardiovascular mortality and the presence of cardiovascular disease[21]. AT- T and its close association with AT-SR and CAD and CAD major risk factors give rise to the hypothesis that the study of AT US may be associated with the presence of MAC. To our knowledge, there is no study in the literature that evaluates the relationship between AT -T and AT-SR and MAC. Therefore, in our study, we aimed to investigate the significance of AT -T and AT-SR in examining AT US and SE for the detection of patients with MAC.

MATERIALS AND METHODS

Study population

Between March 2020 and September 2021, 122 patients with MAC were screened. Twenty-two patients were excluded, including 2 patients with mobilization problems, 7 patients with peripheral artery disease, 5 patients with aortic valve disease, 4 patients with heart failure, 3 patients with active thyroid disease, and 1 patient with active infection. According to the exclusion criteria, 100 patients (65 females, 35 males, and a mean age of 64.7 ± 12.1 years) with MAC and 50 control subjects (32 females, 18 males, and a mean age of 63.2 ± 12.8 years) with similar cardiovascular risk factors were included in the study. Because there is no study in the literature examining the main objective of the study, the pilot study of 10 subjects each was found to have less variation in the control group than in the patient group. For this reason, it was calculated that 1 control should be taken for 2 patients and 100 subjects in the patient group and 50 subjects in the control group should be included at 5% error and 80% power. The study was conducted in Adana City Training and Research Hospital. In addition to routine laboratory examinations, patients underwent US examination for AT using B-mode and SE methods. The study was conducted in accordance with the recommendations of the Declaration of Helsinki for biomedical research involving human subjects, and the protocol was approved by the Ethics Committee of the institution (Adana City Training and Research Hospital Clinical Research Ethics Committee. No: 12/02/2020: 50-718). All patients were informed about voluntary consent, and written informed consent was obtained.

All patients were asked about risk factors after a detailed physical examination. Age, sex, DM, HT, HL, and smoking were recorded as patient demographic data. Patients' height and weight were measured, and body mass index (BMI) was calculated.

Laboratory tests

Complete blood count, lipid panel and other biochemical tests, and creatinine levels were measured in all patients on admission. Venous blood samples of the patients were collected after a fasting period of 8-12 hours. Routine laboratory parameters (glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, complete blood count) were analyzed in all participants. Serum lipid levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured using xylidine blue and a colorimetric end-point method.

Yellow Vacutainer biochemistry tubes with caps were used for biochemical parameters. The biochemistry tubes were centrifuged at 4000 rpm for 10 minutes in a Nuve 1200R centrifuge to obtain serum. Creatinine; measured as a kinetic color assay (Jaffe method) on the Beckman Coulter AU5800 instrument (measured at a wavelength of 520/800 nm). Hemogram samples were collected in purple tubes with K2 EDTA caps. Samples were analysed using a fully automated Beckman Coulter UniCel DxH 800 (flow cytometric method). Commercially available kits from the companies to which the instruments belong were used for all parameters.

Echocardiographic examination

Echocardiographic examinations of patients were performed with standard techniques using the EPIQ 7 device (Philips Healthcare Andover MA, USA), which is used in the noninvasive echocardiography laboratory of our hospital. According to the guidelines of the American Society of Echocardiography, patients were monitored and left-sided, then standard parasternal long and short axis images were acquired [22]. The diagnosis MAC was made by two experienced echocardiographers (AY, MK) with at least 10 years of experience in echocardiography. MAC usually presents as an echo-dense, irregular appearance associated with the mitral valve annulus, and there is usually acoustic shadowing. The M-mode echocardiography method was used to visualize the appearance of the echodense band associated with the posterior mitral leaflet and its motion with the left ventricular (LV) free wall. MAC localization in the LV posterior wall and the posterior mitral leaflet angle was clarified by 2D echocardiography technique. MAC severity was qualitatively classified as mild, moderate, and severe. Mild MAC was determined as limited increase in the echo density of the mitral annulus. Moderate MAC was determined as marked echo density affecting one-third to one-half of the annular circumference. Severe MAC was defined as marked echo density affecting more than half of the annular circumference or invading the LV inflow tract. Maximum anterior to posterior MAC thickness is also used to assess MAC severity, with a value < 1 mm, 1 - 4 mm and > 4 mm defining mild, moderate and severe MAC, respectively [23].

Achilles tendon ultrasound examination

Ultrasound examination of the Achilles tendon was performed by two experienced radiologists (BCP, ASK) using a high-resolution ultrasound machine (Philips EPIQ 7, Philips Health Care, Bothell, WA, USA) and a high-resolution linear probe of 12-5 MHz. One of the radiologists' thesis topics was elastography examination in breast lesions (BCP). For the AT B-mode US examination, patients were in the lateral decubitus position and the knee was flexed 90°, and measurements were taken at the level of the medial malleolus in the transverse plane. Achilles tendon thickness (AT -T) was determined by measuring the widest anteroposterior distance from AT and AT width (AT -W) was determined by measuring the widest distance from the medial-lateral wall of the tendon (Figure 1) [24].

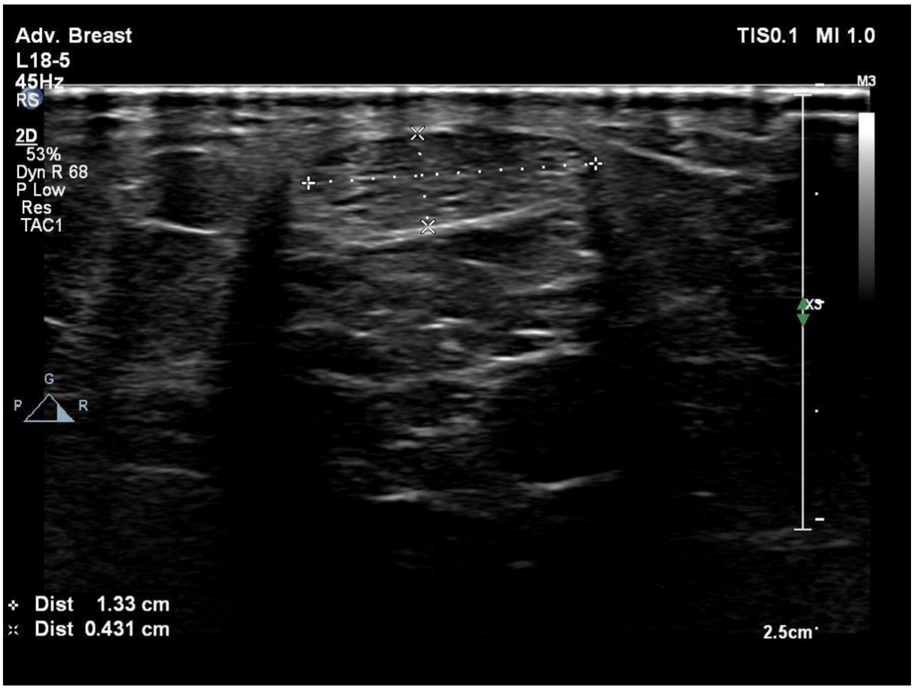

Figure 1. Measurement of Achilles tendon thickness by B-mode ultrasonography. Achilles tendon thickness was measured by evaluating the anteroposterior diameter in a transverse view at the level of the medial malleolus.

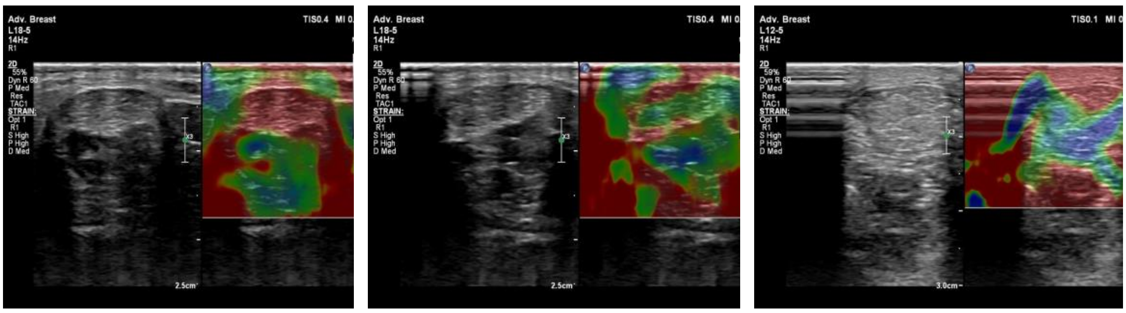

Figure 2. Color elestography of the Achilles tendon in different grades: (a) grade 1; red (hardest tissue) to yellow (hard tissue), (b) grade 2; green (intermediate tissue), and (c) grade 3; blue (soft tissue).

After B-mode US examination, real-time examination AT SE was performed in the same position with evaluation and measurements in the transverse plane via images. Brief, repetitive manual compressions were applied to the Achilles tendon, avoiding anisotropy. Compression intensity and uniformity were standardized using the pressure chart displayed on the screen, and after at least three compression-relaxation cycles, the best image was determined and a SE evaluation was performed. The color scale described in the literature and elastographic findings defined for SR were used [25-26]. For Achilles tendon hardness, the color scale in our device was used, and according to the color scale of SE and AT, grade 1; red (the hardest tissue) or yellow (hard tissue), grade 2; green (intermediate tissue), and grade 3;

automatically determined by the device as blue (soft tissue) (Figure 2a, b, c). AT-SR measurement was calculated with freehand technique using light compression and decompression method by comparing with Kargers pad on the posterior part of the tendon. During the examination, the region of interest (ROI) was first placed in the reference fat tissue (A), then the second ROI was placed in AT (B), and the strain ratio (B/A) was automatically measured in the US device. In this way, AT-SR was evaluated semiquantitatively by comparing it with the adjacent reference tissue. Three consecutive measurements were made for each AT, and the two values of AT were averaged.

Statistical analysis

All analyzes were performed with the SPSS 22.0 statistical software package (Chicago, IL, USA). Whether or not the distribution of continuous variables was normal was assessed using the Kolmogorov-Smirnov test. Continuous variables in group data were expressed as mean ± standard deviation, and categorical variables were expressed as numbers and percentages. Student t tests and one-way tests ANOVA were used to compare continuous variables. The chi-square ($\chi 2$) test was used to compare categorical variables. To independently identify patients with MAC, parameters with a $p <$of 0.01 were included in the multivariate model in univariate analyzes, and multivariate logistic regression analysis was performed. ROC curve analysis was used to evaluate the performance of these markers in detecting MAC and to determine cutoff values.

RESULTS

In the study, 122 patients with MAC were screened. Twenty-two patients were excluded, including 2 patients with mobilization problems, 7 patients with peripheral artery disease, 5 patients with aortic valve disease, 4 patients with heart failure, 3 patients with active thyroid disease, and 1 patient with active infection. According to the exclusion criteria, 100 patients were included in the study.

Table 1. Baseline characteristics of the study population with and without MAC

	Patients with MAC *n*=100	Patients without MAC *n*=50	p
Age (years)	64.7 ± 12.1	63.2 ± 12.8	0.501
Gender (male)	35	18	0.522
Office systolic BP (mmHg)	128 ± 21	121 ± 19	0.066
Office diastolic BP (mmHg)	81± 14	76 ± 11	0.051
Heart rate (beat/min)	76 ± 6.8	74 ± 6.8	0.074
Weight (kg)	80 ± 13	79 ± 12	0.370
Height (cm)	167 7.7	166 ± 9.6	0.672
BMI (kg/m^2)	29 ± 5.2	28 ± 4.4	0.546
Smoking, n (%)	78(78%)	39 (78%)	0.578
Hypertension, n (%)	46 (46%)	24 (48%)	0.703
Diabetes mellitus, n (%)	69 (69%)	32 (64%)	0.331
Hypercholesterolemia, n (%)	68 (68%)	38 (76%)	0.322
Glucose (mg/dL)	131.2 ± 40.9	112.5 ± 18.8	0.055
Creatinine (mg/dL)	0.89 ± 0.28	0.1 ± 0.29	0.684
Alanine transferase (u/L)	25 ± 13	24 ± 12	0.850
AST (u/L)	23 ± 14	25 ± 13	0.237
Total Cholesterol (mg/dL)	194 ± 43	185 ± 42	0.250
LDL Cholesterol (mg/dL)	128 ± 31	129 ± 33	0.824
HDL Cholesterol (mg/dL)	43 ± 12	42 ± 11	0.729
Triglyceride (mg/dL)	179 ± 87	177 ± 73	0.896
White blood cell count (1000/mm3)	7.5 ± 2.4	7.9 ± 2.1	0.317
Hemoglobin (g/dL)	13.4 ± 1.9	13.5 ± 2.3	0.892

BMI: Body mass index, BUN: Blood urea nitrogen, MAC: Mitral annulus calcification, HDL: High-density lipoprotein; LDL: low-density lipoprotein.

AT ultrasonography was successfully performed in 100 patients (65 females, 35 males, mean age 64.7 ± 12.1) with echocardiography who had MAC and 50 control groups (32 females, 18 males, mean age 63.2 ± 12.8) with similar cardiovascular risk factors. Patients were divided into two groups, those with and those without MAC, and all parameters were compared, and the parameters that determined the group of patients with MAC were assessed.

Clinical, demographic, and laboratory parameters were compared between the groups of patients with and without MAC. These parameters were similar between the groups (Table 1).When comparing AT -T and AT length between patient groups with and without MAC, patients with MAC had higher AT -T and AT lengths (Table 2). AT-SR values were significantly higher in patients with MAC (Table 2) (Figure 3a,b). In addition, when the elastographic color grade of the Achilles tendon determined by SE was examined, it was found that the presence of grade I (hard tissue or hardest) and grade III (soft tissue) were higher and lower, respectively, in patients with MAC (Table 2).

Table 2. B-mode ultrasonography and strain elastography imaging of the Achilles tendon in a patient with and without MAC

	Patients with MAC ***n*=100**	**Patients without MAC** ***n*=50**	**p**
Achilles tendon thickness (mm)	5.73 ± 1.06	4.97 ± 1.14	**<0.001**
Achilles tendon length (mm)	15.6 ± 1.40	14.8 ± 2.25	0.004
Achilles elastographic color grade I-II-III,(n)	2–8–90	12–30–5	**<0.001**
Achilles tendon strain ratio	2.64 ± 1.36	1.52 ± 0.96	**<0.001**

MAC: Mitral annulus calcification

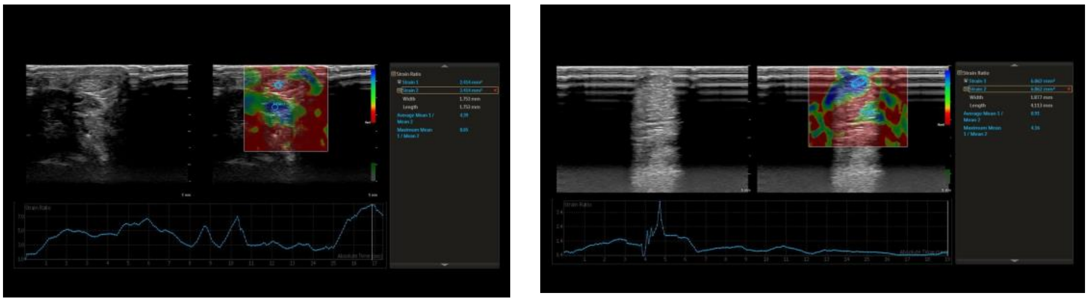

Figure 3. Measurement of Achilles tendon strain ratio by strain elastography. Measurements of the strain ratio at the level of the medial malleoli (region of interest) and the reference region (Kargers adipose tissue behind the AT) of (a) a MAC patient and (b) a non MAC patient. The software of the ultrasound machine calculates the strain ratio.

In multivariate logistic regression analysis, we found that the AT-SR and AT -T values independently determined the risk for MAC (Table 3). Each 1-mm increase in the AT -T value and each 0.1-unit increase in the AT-SR value increased the risk for MAC by 69.9% and 12.7%, respectively (Table 3).

Table 3. According to multivariate regression analysis, independent risk factors for the occurrence of MAC

	Odds Ratio	**95% Confidence Interval**	**p**
Achilles tendon thickness (mm)	1.699	1.137– 2.539	**0.010**
Achilles tendon strain ratio (each 0.1 increase)	1.127	1.066 – 1.192	**<0.001**

MAC: Mitral annulus calcification

In the ROC analysis of Achilles tendon thickness and AT-SR values to identify patients with MAC, the areas under the ROC curve were 0.684 and 0.819, respectively ($p < 0.05$) (Table 4). Achilles tendon thickness and ROC curve for AT-SR are shown in Figure 4. With a cut-off value of 5 mm for Achilles tendon thickness and a cut-off value of 1.25 for AT-SR, it was found that the probability of having MAC was determined with the best sensitivity and specificity (Table 4).

Table 4. ROC curve analysis for predicting MAC

Variable	AUROC Curve	p	Cut-off	Sensitivity	Specificity
Achilles tendon thickness	0.684 (0.587–0.781)	**<0.001**	5 mm	91.0%	67.3%
Achilles tendon strain ratio	0.819 (0.746–0.893)	**<0.001**	1.25	94.1%	76.2%

MAC: Mitral annulus calcification

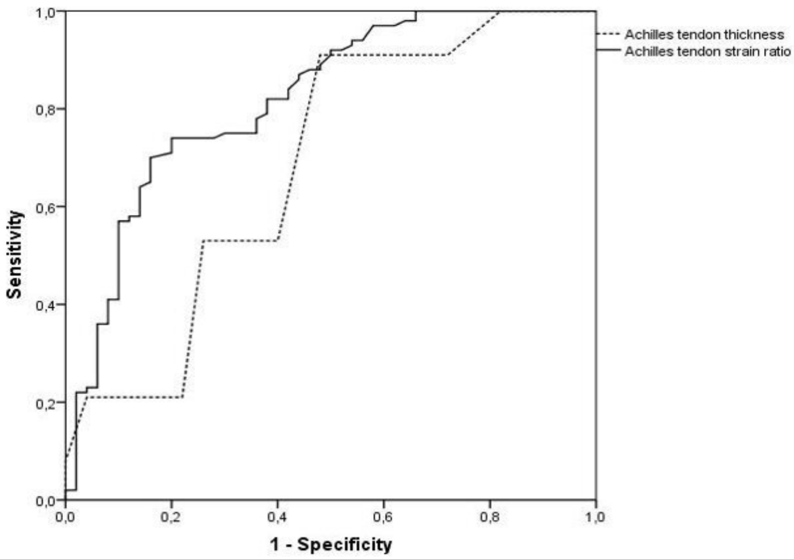

Figure 4. ROC curve analysis of Achilles tendon thickness and strain ratio to predict MAC.

The severity of MAC was assessed by echocardiography, and the numbers of patients with mild, moderate, and severe MAC were 16, 57, and 27, respectively. Only the AT-SR values differed between the groups of clinical and US parameters according to the severity of MAC ($p < 0.001$). The AT-SR values were 1.47 ± 0.42, 2.28 ± 0.63, and 4.11 ± 1.65 in patients with mild, moderate, and advanced MAC, respectively ($p < 0.001$).

DISCUSSION

The most important finding of our study is that the increased AT-SR value determined by AT SE independently determines the risk of having MAC. To the best of our knowledge, our study is the first to show an association between AT-SR and AT -T determined by SE and the presence of MAC. When the AT-SR value is taken as > 1.25, the presence of MAC is detected with acceptable sensitivity and specificity. In addition, the AT-SR value was found to increase significantly with increasing MAC severity in our study.

Because the AT is the most easily accessible tendon, it has been studied radiologically in many diseases, including aging. The best measurement technique for AT -T is US [27]. SE, a new US technique, that provides important insights into the elastic properties and stiffness of tissues [6]. This study was performed to evaluate the elastic properties of AT [13-16].

It has been clearly shown that CAD and major risk factors for CAD (smoking, DM, obesity, HL and advanced age) increase AT-SR. The pathophysiology of changes in AT -T and AT-SR caused by CAD risk factors is very similar to coronary atherosclerosis in patients with CAD [19,27-29]. The mechanism of formation of MAC is also associated with CAD risk factors, peripheral vascular disease, aortic atheroma, CAD, and carotid atherosclerosis [3,30-32]. Therefore, AT-SR and AT -T assessments may be noninvasive assessments in MAC determination. Our study ensured that cardiovascular risk factors were similar in patients with and without MAC, so cardiovascular risk factors did not affect the incidence of MAC. In this way, the MAC entity is directly related to the AT-SR.

With age, abrasion and dysfunction occur in all parts of the body [33]. With age, similar to changes in the vessel wall, there is an increase in the extracellular matrix component [34]. AT elastic properties decrease with age. A recent study found an increase in AT-SR with age [13]. MAC is a degenerative and age-related process. Age is an independent parameter in determining the presence of MAC in all ethnic groups [3,35]. In our study, controls were in a similar age group as the patient group with MAC. Therefore, the influence of age on the determination of MAC and AT-SR was not investigated.

It was found that there was a close association between advanced age and cardiovascular disease, as well as MAC and the increase in AT stiffness, which are associated with cardiovascular risk factors. In addition, the change in severity of the two pathological conditions was also found to be related [27-29,30-34]. This situation raised the suggestion that degenerative and calcifying changes in MAC and Achilles skin may be similar.

In a recent study by Koc AS et al [20], it was found that the increase in AT-SR independently determined the presence of CAD. In this study, it was reported that a simple and reliable diagnosis of an important disease such as CAD can be helpful in diagnosing AT SE. In our study conducted in the light of this study, it was determined that the AT-SR value obtained by AT SE examination increased in MAC patients as well.

Although our study is adequate in terms of the number of patients compared with the other AT US studies, it has several important limitations. The SR obtained with SE is an operator-dependent examination. In our study, there were two radiologists, one of whom had SE experience and one of whom had written a thesis on the subject. However, if it had been the third examiner, there could have been a clearer result in the measurements that the two radiologists found different. We did not evaluate the patients' physical activities in the past. This may have a positive or negative impact on the AT-SR and AT -T. Although our findings with SE were related to tissue stiffness, histopathologic examination was not performed because this is an invasive procedure. Previous studies have shown that SE and histological examination are closely related [36]. SE method was used in our study and it is a semiquantitative method according to shear wave elastography technique. There is one study in the literature that examines the relationship between the shear wave elastography findings of AT and AT rupture [37]. Shear wave elastography is a quantitative method, and data from studies in which AT was evaluated with shear wave elastography may also be useful. In some studies, the Achilles tendon was divided into three areas when examined at SE and AT-SR was reported separately for each area [13-15]. In these studies [13-15], a similar SR was reported for all regions. Therefore, we evaluated only the medial malleolar and transverse planes in our study. Another important reason was that reporting different values from 3 regions led to conceptual confusion with different cutoff values. Therefore, when using our data, it should be noted that measurements were made at the level of the medial malleolus and in the transverse plane.

In coclusion, the AT-SR value obtained by SE is a simple and practical, reliable and reproducible, and noninvasive parameter that can be used to identify patients with MAC. It was hypothesised that patients with AT-SE > 1.25, especially when examining the Achilles SE, should be followed more closely for the possibility of MAC. The increase in AT-SR value, which was previously associated with cardiovascular disease, may be an investigation that can be used in the follow-up of cardiovascular disease.

Yazar Katkıları: Çalışma konsepti/Tasarımı: BÇP, AY; Veri toplama: BÇP, AY; Veri analizi ve yorumlama: BÇP, AY; Yazı taslağı: BÇP; İçeriğin eleştirel incelenmesi: BÇP, AY; Son onay ve sorumluluk: BÇP, AY; Teknik ve malzeme desteği: BÇP, AY; Süpervizyon: BÇP, AY; Fon sağlama (mevcut ise): yok.
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