

# The role of vascular elastography and carotid artery intima media thickness methods in the determination of non-syndromic ascending thoracic aortic aneurysm

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## Abstract

**Aim:** The role of atherosclerosis in the pathogenesis of ascending thoracic aortic aneurysms is still uncertain. Ultrasonic elastography is a new diagnostic method, the use of which has diversified considerably in recent years. An increase in intima media thickness in the carotid arteries is an early finding of atherosclerosis. Our purpose was to investigate the effect of atherosclerosis in the development of ascending thoracic aortic aneurysms and to be able to recommend a non-invasive and inexpensive scanning method aiming at early diagnosis.

**Material and Methods:** Thirty-three patients with ascending thoracic aortic aneurysms (aTAA group) and 40 patients with normal measurement (control group) values were included in the study. The carotid artery intima media thickness of carotid arteries were measured using B mode ultrasonography. Elastographic examination of the intima-media was then performed.

**Results:** Body mass index, past smoking status, hypertension, presence of coronary artery disease and hyperlipidemia were higher in the aTAA group than in the control group ( $p < 0.05$ ). No significant difference was determined between these two groups' ultrasonic elastography or intima media thickness in the carotid arteries values ( $p < 0.05$ ).

**Conclusions:** Our findings suggest that the effect of atherosclerosis in the pathogenesis of ascending thoracic aortic aneurysms is limited. Vascular ultrasonic elastography and intima media thickness determination in the carotid arteries appear not to be effective in the evaluation of ascending thoracic aortic aneurysms.

**Keywords:** Aneurysm; Atherosclerosis; Intima-Media Thickness; Vascular Elastography.

## INTRODUCTION

Ascending thoracic aortic aneurysms (aTAA) generally produce no clinical findings before causing cardiovascular emergencies, such as dissection or rupture. The pre-hospital mortality rate of these emergency conditions is 40%, increasing by 1% for every hour without surgical intervention (1,2). Despite advances in surgical techniques and perioperative care conditions, the operative mortality rate is 15-30% (2). The silent course of the disease and the lack of an effective screening method for early diagnosis make it difficult to determine the true incidence of aTAA and to prevent acute events with attendant high mortality (3,4). Diameter measurement alone is insufficient in the prediction of emergency events, since dissection is frequently reported in patients with a mean aortic

diameter  $< 5.0$  cm, hence better markers are needed for a more accurate surgical timing (1,4).

Atherosclerosis plays an important role in the pathogenesis of numerous vascular diseases. Despite the information obtained to date, the pathophysiology of aTAA and the effect of atherosclerosis on the development of aneurysm are still not well understood (2,4,5). Population-based studies have shown a correlation between the severity of atherosclerosis in an arterial region and involvement of other arteries (6,8). Methods developed for the early identification of arterial diseases in healthy-appearing individuals have therefore focused on the peripheral arteries, and particularly the carotid arteries (8). An increase in carotid artery intima media thickness (CIMT) is regarded as an early finding of generalized atherosclerosis (3,6,7).

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Although CIMT screening is not recommended for risk assessment in cardiovascular diseases in the most recent European Society of Cardiology (ESC) guideline, CIMT investigation may nevertheless provide an opportunity for clinicians to assess subclinical atherosclerosis in the vessel wall (8,10). Previous studies have investigated the relation between increased CIMT and various vascular diseases, such as coronary artery disease (CAD), peripheral artery disease (PAD), intracranial arterial aneurysms, and abdominal aortic aneurysms (AAA) (9,10,11,12). However, the number of studies concerning aTAA is very small (13).

Ultrasound elastography (EUS), a novel diagnostic technique, was developed in recent years on the basis of the fact that pathological processes alter tissue elasticity (14). EUS is used in the differential diagnosis of breast and thyroid lesions, in the differentiation of benign and malignant lymph nodes, in the staging of hepatic fibrosis, in the characterization of focal pancreatic lesions, and to differentiate active inflammation and in bowel wall lesions and fibrotic stenosis (15-20). Our investigation of the literature showed that studies of EUS in the context of atherosclerotic vascular diseases have focused on unstable plaques in the carotid arteries and on determining the risk of stroke (21,22). However, we encountered no EUS studies investigating the systemic vascular effects of atherosclerosis.

This study investigated vascular EUS and CIMT values in patients with aTAA. Our aim was to investigate the effect of atherosclerosis on the development of aTAA and to be able to recommend a non-invasive and inexpensive screening method aiming at early diagnosis.

## MATERIAL and METHODS

**Study population:** The study was carried out with the approval of the local ethical committee (23618724), and informed consent was obtained from the participants. The records of all patients undergoing thoracoabdominal computerized tomography (CT) with contrast enhancement at the Kanuni Education and Research Hospital, Turkey, between October 2015 and July 2016 were examined. Aortic diameter measurements were performed from the ascending, arch and descending thoracic aorta and abdominal segments.

Aortic diameter  $\geq 40$  mm was regarded as aneurysm. Patients' demographic data, body mass index (BMI) values, hypertension (HT) (blood pressure  $\geq 140/90$  mm Hg in non-diabetic subjects, and  $\geq 130/80$  mm Hg in diabetics or subjects receiving antihypertensive therapy), hyperlipidemia (subjects with low density lipoprotein  $\geq 135$  mg/dl or receiving lipid lowering therapy), diabetes mellitus (DM) (fasting plasma glucose  $\geq 126$  mg/dl, non-fasting plasma glucose  $\geq 200$  mg/dl or subjects receiving antidiabetic drugs), presence of CAD and cerebrovascular disease (CVD), smoking status and data concerning drugs used were recorded.

Patients with diseases leading to structural impairment in the vascular wall, such as Marfan and Ehler Danlos

syndromes, with chronic renal failure (serum creatinine  $\geq 2.0$  mg/dl or receiving dialysis), bicuspid aortic valve, advanced regurgitation in the aortic and/or mitral valve, PAD, arcus aorta or descending thoracic aneurysm, AAA, a history of cardiac and/or aortic surgery, endovascular intervention or neck surgery, atherosclerotic plaque in the carotid artery lumen were excluded from the study. Forty patients with measurement values within normal limits were enrolled in the control group and 33 patients with ascending thoracic aortic aneurysm in the aTAA group. Sonomorphological examination of both carotid arteries and their branches of the 73 patients included in the study was performed with B mode ultrasonography (US), and CIMTs were measured. Elastographic examination of the intima media was subsequently performed.

**Radiological evaluation:** An Aplio 500 US machine (Toshiba Medical Systems, Co, Ltd, Ottowara, Japan) with linear 4.8-11 MHz transducers and elastography software was used. All examinations were performed by one of two radiologists (AAK or GB) with more than 10 years' experience of carotid Doppler sonographic imaging and blinded to clinical findings, laboratory results, early clinical suspected differential diagnosis of aneurysms and patients' final diagnoses.

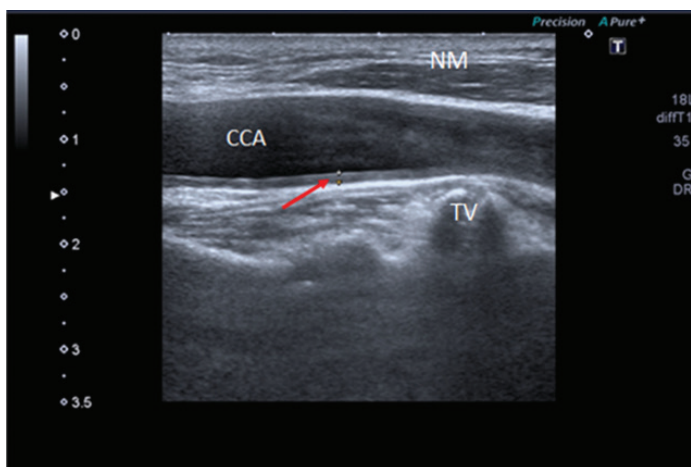
**Ultrasound imaging:** US examination in this study started with gray scale imaging. The patient was placed in a supine and slightly extended position over a special wheeled bed. B mode sonographic evaluation started with the bilateral common carotid arteries (CCA). Following standard transverse and longitudinal evaluation of the carotid system, we performed Doppler sonographic imaging of the carotid system. The right common carotid artery was examined with the head turned away from the side of interest, and the transducer was replaced so that the near and far walls of the common carotid artery were parallel to the transducer foot print, and the lumen measurement was maximized in the longitudinal plane. A region 1 cm proximal to the carotid bifurcation was identified, and the IMT of the far wall was evaluated. The IMT measurement was taken from four contiguous sites at 1-mm intervals, and the mean of the four measurements was used for analyses (Figur 1).

Localized structures narrowing the arterial lumen by 1.5 mm or more were defined as atherosclerotic plaques (23), and these patients were excluded from the analysis, since our aim was to investigate the relationship between aTAA and CIMT elastography extensively from atherosclerotic plaque elastography. Twenty-nine patients with atherosclerotic plaque in the carotid artery lumen were also excluded from the study. The blood flow in both carotid arteries was observed using color Doppler US, and blood flow parameters of bilateral carotid artery peak systolic velocity and end-diastolic velocity were measured using spectral analysis.

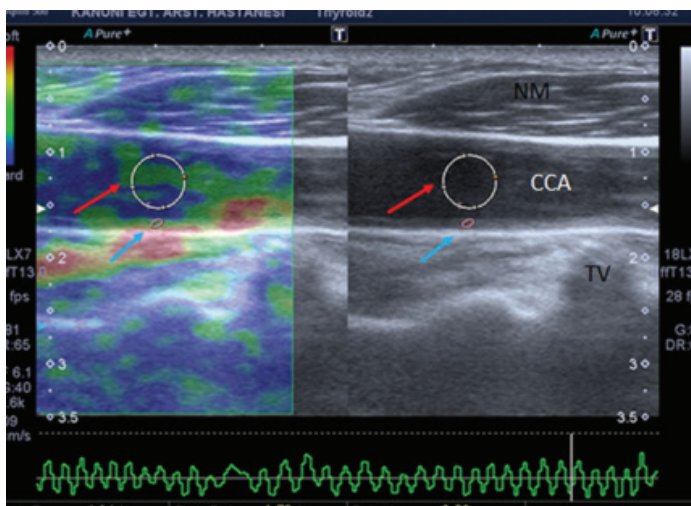
**Elastography imaging and image analysis:** During gray scale ultrasonography (US), the carotid arteries were evaluated and a region of interest (ROI) for elastography

was identified. Once the elastography mode is selected, the scale of colors is superimposed over the gray-scale image. The gray-scale image appears on the right side of the screen and the sonoelastogram on the left. Light compression was applied to the carotid artery region in the sagittal plane using the transducer. At the same time, elastographic images were displayed over the B-mode image on the monitor.

Multiple elastographic images were evaluated and the technically optimal elastogram was selected in order to define the elasticity score (Figur 2).



**Figure 1.** B mode sonographic image depicting carotid intima-media measurement (red arrow), CCA; common carotid artery, NM; neck muscles, TV; transverse process of cervical vertebrae



**Figure 2.** Measurement of Elastography. The big white circle (red arrow) represents blood whereas smaller pink one (blue arrow) represents intima media. CCA; common carotid artery, NM; neck muscles, TV; transverse process of cervical vertebrae

In terms of color codes on elastographic images, blue is associated with harder regions, red with softer regions and green with moderately harder regions of the intima-media. The elastographic color scale is related to the degree of stiffness: red (soft tissue), green (intermediate stiffness), and blue (inelastic tissue). For classification, we used a 4-point modified Ueno scale (15).

Elasticity score (ES) I is associated with predominantly green color with a red and yellow mosaic pattern, ES II with predominantly green color with a few areas of blue mosaic appearance, ES III with a predominantly blue color with some areas of green and a green and blue mosaic pattern, while in ES IV most of the intima media exhibit significantly increased stiffness, with a blue color. In addition to real-time elastographic evaluation, intima-media strain can be evaluated using numerical strain values and cross-checked with a correlation of radiofrequency signals.

We selected two consecutive region of interest circles as a target for comparing intima-media with the ipsilateral carotid artery for determining the control stiffness value. Both ROIs contained the same amount of intima-media and carotid artery. Before calculating the strain ratio we ensure that the jugular vein did not appear on the B-mode image. We obtained four gray scale images and elastogram and strain measurements for both carotid arteries. Following the examination we selected the most technically perfect image for the evaluation of carotid artery color code grading and stiffness. This selected elastogram was considered valid.

Statistical analysis: Data were analyzed on Statistical Package for the Social Sciences (SPSS) software (version 23 for Windows) (SPSS Inc., Chicago, IL, USA). All differences associated with a probability of 0.05 or less were considered statistically significant. Descriptive statistics are presented as number and percentage and continuous variables as mean  $\pm$  standard deviation. Categorical data were analyzed using the chi-square or Fisher's exact tests and continuous variables using the independent samples t- test. Statistical tests used and p-values were given in detail in table form in the results section.

## RESULTS

Thirty-three subjects, 22 of whom were male, were included in the aTAA group and 40 subjects, 29 male, in the control group. Basic characteristics of the study group and comparisons thereof were shown in Table 1. No significant difference was determined between the groups in terms of gender distribution, age, current smoking status or presence of DM and CVD ( $p > 0.05$ ).

BMI, past smoking status, presence of HT, hyperlipidemia and CAD were significantly higher in the aTAA group ( $p < 0.05$ ). As shown in Table 2, no significant difference was observed between the aTAA and control groups in terms of CIMT ( $0.77 \pm 0.19$  vs  $0.71 \pm 0.33$ ,  $p = 0.338$ ) or strain ratio values ( $0.56 \pm 0.56$  vs  $0.70 \pm 0.60$ ,  $p = 0.320$ ).

The groups' ES values were shown in Table 3. Since no patients in the aTAA group and only one in the control group had ES values of 4, analysis was performed for ES values of 1, 2 and 3. Accordingly, the presence of aneurysm was found to have no statistically significant effect on ES ( $2 \times 3$  Fisher's exact test p value: 0.721).

**Table 1. Analysis of the study population**

	Control group (n=40)	aTAA group (n=33)	P value
Gender (% of males)	72.50	66.70	0.617 <sup>b</sup>
Age (years)	68.65	67.70	0.745 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	27.62	29.90	0.031 <sup>a</sup>
Smokers (%)	22.50	24.20	0.861 <sup>b</sup>
Past smokers (%)	20.00	42.40	0.038 <sup>b</sup>
Hypertension (%)	37.5	72.70	0.003 <sup>b</sup>
Hyperlipidemia (%)	5.00	27.30	0.018 <sup>c</sup>
Diabetes mellitus (%)	85.00	84.80	1.000 <sup>c</sup>
CAD (%)	17.5	39.40	0.037 <sup>b</sup>
CVD (%)	5.00	15.20	0.233 <sup>c</sup>

<sup>a</sup>TAA: Ascending Thoracic Aortic Aneurysms, BMI: Body Mass Index, CAD: Coronary Artery Disease, CVD: Cerebrovascular Disease,

<sup>a</sup>Independent samples t-test,

<sup>b</sup>Chi square test,

<sup>c</sup>Fisher's exact test

**Table 2. CIMT and strain ratio values**

CIMT and strain ratio values in the control and aneurysm groups			
	Control group (n=40)	aTAA group (n=33)	P value
CIMT (Mean±SD)	0.71± 0.33	0.77± 0.19	0.338 <sup>a</sup>
Strain ratio (Mean±SD)	0.70± 0.60	0.56± 0.56	0.320 <sup>a</sup>

**CIMT: Carotid Intima Media Thickness, aTAA: Ascending Thoracic Aortic Aneurysms, SD: Standard deviation**

<sup>a</sup>Independent Samples t-test,

**Table 3. Elasticity score values**

Elasticity score values in the control and aneurysm groups <sup>d</sup>					
	ES 1 n (%)	ES 2 n (%)	ES 3 n (%)	ES 4 n (%)	Total n (%)
Control group	17 (42.5)	17 (42.5)	5 (12.5)	1 (2.5)	40 (100.0)
aTAA group	11 (33.3)	17 (51.5)	5 (15.2)	0 (0.0)	33 (100.0)

**ES: Elasticity score, aTAA: Ascending Thoracic Aortic Aneurysms**

<sup>d</sup>2x3 Fisher's exact test p value: 0.721

ES 4 is omitted and then <sup>d</sup>2x3 Fisher's exact is applied

## DISCUSSION

The study findings may be summarized as follows: i) high BMI, past history of smoking and the incidence of hyperlipidemia, HT and CAD were higher in the patients with aTAA than in the control group. ii) No difference was determined between the aTAA and control groups in terms of CIMT values. iii) No difference was determined between the aTAA and control groups in terms of EUS values. iv) No correlation was determined between IMT and EUS values. In agreement with the literature, atherosclerotic risk factors such as high BMI, smoking, hyperlipidemia and HT were higher in the aTAA group than in the control group in this study (2-5). Atherosclerosis in aortic aneurysms is closely associated with increased medial degeneration and aortic dissection (24). The fragmentation of elastic fibers constitutes a significant part of the thoracic aortic remodeling process that accompanies aging. Calcific and

atherosclerotic lesions have been reported to accompany this fragmentation involved in the pathogenesis of aneurysm (25). Atherosclerosis begins damaging the arterial wall by causing asymptomatic changes. Early atherosclerotic changes in the arterial wall progress rapidly to severe lesions under the effect of cardiovascular risk factors (9,10,25). Currently Doppler US or angiography are generally used for the evaluation of arterial diseases. However, these techniques provide no information about pathological changes in the arterial wall prior to the formation of lesions. The evaluation of intima media thickness (IMT) using US was developed in order to be able to investigate the walls of superficial arteries such as the carotid in a detailed and non-invasive manner. The latest ESC guideline does not recommend CIMT for cardiovascular disease risk assessment (8).

Nonetheless, numerous studies have reported that CIMT is a valuable technique for evaluating systemic atherosclerosis in the early period (3,9-11,13). Using this method, the damage caused by atherosclerosis in the arterial wall can be evaluated even in the absence of a lesion causing changes in the lumen (3). CIMT values have been shown to be compatible with histological findings of atherosclerosis (26). Studies have described CIMT as a non-invasive, rapid, easily repeatable, economical and useful method of determining atherosclerosis in the early period (9,11,12,27,28).

Although the relation between CIMT and various atherosclerotic vascular diseases such as CAD, PAD and CVD has been clearly revealed the findings of studies investigating CIMT in aneurysmal diseases are inconsistent (9-12). One study reported that CIMT values in patients with AAA and PAD increased at a similar rate to those of healthy volunteers (29). Studies maintaining the opposite, however, have reported similar CIMT values in patients with AAA to those in healthy volunteers but significantly lower values than those in patients with PAD (10,30). Authors reporting lower CIMT values in AAAs compared to PAH have interpreted those findings as meaning that atherosclerosis is a basic pathological factor in the development of PAH, but that its effect in the development of aneurysm is limited. They also stated that atherosclerosis is only one component of the complex pathophysiological mechanisms in the development of aneurysm. Our review of the literature revealed only one study investigating CIMT in aTAA. Hung et al. compared the mean CIMT values of 52 patients with aTAA and a 29-member control group. They determined significantly lower CIMT values in the aTAA group, independently of atherosclerotic risk factors (age, BMI, gender, family history, smoking, dyslipidemia, race, DM and HT) compared to the control group (0.50±0.13mm vs 0.60±0.11 mm, p= 0.0002). Those authors therefore suggested that the presence of aTAA significantly reduces the development of systemic atherosclerosis. In addition, they reported that proaneurysmal genetic mutations provided protection against atherosclerosis and that it was important for these mechanisms to be understood in order to develop

protective therapeutic strategies against atherosclerosis (13). In contrast to Hung et al. during comparison of CIMT values between the groups in our study, atherosclerotic risk factors, known to play an important role in the etiology of aTAA, were not excluded. In agreement with the information in the literature, smoking, HT and hyperlipidemia levels in the aTAA group were significantly higher than those in the control group (4,5). We attributed the mean CIMT values in our aTAA group being 0.27 mm higher than the patients with aTAA in Hung et al.'s study to this. In conclusion, the absence of a statistically significant difference between CIMT values in our aTAA and control groups suggested that atherosclerosis plays a limited role in the pathogenesis of aTAA, and our findings support those of Hung et al.

The EUS technique was first introduced by Ophir et al. in 1991 (14). This is a non-invasive US technique that measures the degree of hardness of tissues. It calculates the response to compression of the distance between two points determined in the longitudinal plain in the tissue under investigation. The aim is to give an idea of tissue hardness. For example, malignant formations are generally hard and do not respond to compression, while benign formations and normal tissues are softer and permit compression. Tissues can be evaluated according to their "strain ratio" and "strain pattern." The strain ratio is obtained by dividing the hardness (strain) of the surrounding normal tissue by the degree of hardness of the investigated tissue. Scoring systems evaluating lesion hardness are generally used for the strain pattern (14-20). The arterial walls of patients with generalized atherosclerosis are observed to lose elasticity and softness during cardiovascular surgical procedures. We therefore hypothesized that EUS might be useful in the assessment of vascular diseases whose etiopathogenesis involves atherosclerosis. However, our review of the literature revealed no EUS studies investigating the systemic effects of atherosclerosis in vascular diseases. Studies on this subject have generally focused on being able to identify risk of stroke and unstable plaque rupture in the carotid artery (21,22). In our study we determined no significant difference in terms of EUS values between the aTAA and control groups. We also observed no correlation between the CIMT values we obtained and the EUS findings. These findings suggested that, like CIMT, EUS is not a method that can be used in the evaluation of atherosclerotic vascular diseases.

There are a number of limitations to this study. First, there is no standard method of assessing CIMT. Studies have measured the carotid artery and internal carotid arteries from various points based on carotid artery bifurcation. In addition, different methods such as taking the highest from bilateral measurements or mean values have been employed. This makes it difficult to establish a working method and to compare previous studies (9,10). Second, there is no screening technique for determining causes of aneurysm of genetic origin, such as Marfan and Ehler-Danlos syndromes. However, these syndromes are very

rare and are seen in young patients. The possibility of their affecting our study population is therefore very low (9). Third, there are no previous EUS studies of the systemic vascular effects of atherosclerosis. There is therefore no standard defined method for evaluating the carotid arteries for this purpose using EUS.

## CONCLUSION

In conclusion, our findings suggest that the effect of atherosclerosis in the pathogenesis of aTAA is limited. CIMT is an important method in the evaluation of systemic atherosclerosis in the early period. However, it appears to have no efficacy in the assessment of aTAA. On the other hand, our findings suggest that EUS cannot be used as a screening technique in the early assessment of aTAA. Wider ranging studies with broader levels of participation are now needed to illuminate the complex mechanisms underlying the development of aTAA.

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