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The Role of the Autonomic Nervous System in Atherosclerosis of the Thoracic Aorta: A Cadaveric Study

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Abstract

Objective: The Autonomic Nervous System (ANS) has been associated with numerous atherosclerosis-induced cardiovascular events, such as myocardial infarction and aortic disease. Although evidence suggests a relationship between autonomic dysfunction and atherosclerotic disease, the underlying mechanisms are still under investigation. The purpose of this study is to investigate the effect of ANS to the development of atherosclerosis and vice versa, in human thoracic aorta.

Methods: An autopsy analysis from three segments of the thoracic aorta was performed; ascending aorta, aortic arch, descending aorta, using 52 unselected adult cadavers (38 male, 14 female-mean age 64.4 years; age range 19-90 years). Subjects were divided in two age groups (<65 years–n=26, >65 years-n=26). Tissue specimens were macroscopically examined and histopathologically divided into 7 grades of scoring for atherosclerosis (ATHERO, from 0=intact, to 6=thrombi formation). The relationship between ANS and atherosclerosis was depicted by further immunohistochemical analysis for detection of neuron terminals onto the aortic wall. All data were evaluated according to the subject's demographic and clinical characteristics.

Results: Total 96.2% of all subjects had atherosclerosis of variable degree in one or more segments. No aneurismal change was found. The presence of atheromas were common in all subjects regardless of age and segment, with atherosclerosis increasing by age; Ascending aorta (r=.571, p<.001), Aortic arch (r=.655, p<.001), Descending aorta (r=.659, p<.001). Hypertension was a significant factor in the development of atherosclerosis in adults>65 years (r=.450, p=.023). In addition, a positive history of hypertension was statistically significant regarding both the presence of atherosclerosis and neuron terminals in all three aortic wall segments; Ascending aorta (p=.037), Aortic arch (p=.046), Descending aorta (p=.045). Furthermore, there was a strong negative correlation between the ATHERO score and the presence of neuron terminals in all three aortic segments; Ascending aorta (r=-.264, p=.041), Aortic arch (r=-.400, p=.003), Descending aorta (r=-.234, p=.047).

Conclusion: Human cadaveric studies are extremely useful in understanding the pathophysiology of ANS, along with clinical and animal studies that are most commonly performed. These data suggest that there is a link between autonomic disfunction and the presence of atherosclerosis in human thoracic aorta, especially when hypertension is present. It is therefore possible that stress-induced hypertension can be considered as a potential risk factor for the development of atherosclerosis.

Keywords: Atherosclerosis; Hypertension; Stress; Sympathetic nervous system; Thoracic aorta; Cadaveric; Neuron terminals

Introduction

The Autonomic Nervous System (ANS) is the major system responsible for maintaining homeostasis, and regulating the responses of acute stress [1]. It consists of two branches: the Sympathetic Nervous System (SNS) and Parasympathetic Nervous System (PNS), two pathways with frequently antagonistic responses, which can also work synergistically or independently to balance the functions of autonomic effector organs [2]. The cardiovascular system includes the heart and blood vessels, which are innervated by both SNS and PNS [3].

Cardiovascular Disease (CVD) is the leading cause of death in the world, accounting for 32% of global mortality in 2012. With new treatment methods developing every year, the prevalence is still increasing [4]. CVD includes a range of diseases that involve both the heart and blood vessels. Many of these conditions, including stroke, peripheral artery disease and Coronary Artery Disease (CAD), result from the formation of atherosclerotic lesions in the vessels [5].

Atherosclerosis is a complex of chronic inflammation of the vessel wall. It primarily affects large elastic arteries (i.e., aorta) and medium-sized muscular arteries (i.e., coronary arteries) and progressively develops degeneration of the vessel wall [6]. The major risk factors for atherosclerosis are Hypercholesterolemia (HC), smoking, and hypertension.

These factors affect the endothelium from the luminal side of vessels. In hypertension, endothelial dysfunction affects the pathologic process through autonomic nervous pathways. However, the mechanisms of this relationship are still unclear. In addition, behavioral factors have also been implicated in both human and nonhuman primate studies. The Autonomic Nervous System (ANS) is considered to be one of these factors that affects the behavior of endothelial function from an extra luminal point of view [7,8].

During the last decade, numerous clinical studies have shown a relationship between modulated autonomic function and CVD. Autonomic dysfunction is associated with an elevated risk of cardiovascular events independent of other traditional risk factors [7]. Although the majority of these studies address the relationship between augmented activity of the SNS and increased risk for CVD [9], there are studies suggesting reduced parasympathetic activity as the main contributor [10]. In addition, studies report that psychosocial stress prospectively could predict cardiovascular mortality and stroke [11].

In summary, there is no consensus in literature as to the relationship between atherosclerosis and the sympathetic nervous system. Although evidence points to an increased risk for cardiovascular mortality in the presence of sympathetic drive, and a possible protective role for increased parasympathetic activity, yet the mediating mechanisms still remain unclear.

The purpose of this study is to investigate the interaction between the ANS and the development of atherosclerosis by examining 52 human thoracic aortas that were obtained from necropsy. The evidence of a potential role of both parametric (i.e., hypertension) and non-parametric (i.e., stress) risk factors for a nerve-driven effect on both inflammation and atherosclerosis, would underline the need for further investigation of this elusive relationship.

Materials and Methods

The study was carried out on thoracic aortas obtained during routine autopsies of 52 cadavers aged from 19 to 90 (mean ± SD, 64.4 ± 16.76) years, in the Laboratory of Forensic medicine and Toxicology of the Aristotle University of Thessaloniki, Greece during a period of one year. The cause of death was obtained from death certificates (Table 1). Information about previous diseases and cardiovascular risk factors was obtained from death certificates and medical records, if available (Table 2). None of the study subjects had a history of known aortic aneurism or stroke. Inclusion criteria were age over 18 years and an autopsy had to be intended. A signed letter of consent was taken from the relatives of the dead bodies. Where consensus could not be reached, third independent review was sought from a Professor of Forensic medicine.

This study was carried out in accordance with the World Medical Association's Declaration of Helsinki.

Cause of death	n (%) N=52	Age in years (mean)	M/F
MI	19 (36.5%)	66.1	16/3
Accident	18 (34.6%)	57.1	13/5
Cancer	11 (21.2%)	67.2	6/5
COPD	4 (7.7%)	67	2/2

MI: myocardial infarction; COPD: chronic obstructive pulmonary disease; F: female; M: male

Table 1: Demographic data and cause of death.

		N=52	N %
Gender	Male	38	73,1%
	Female	14	26,9%
Smoking	Yes	35	67,3%
	No	17	32,7%
Hypertension	Yes	29	55,8%
	No	23	44,2%
CAD	Yes	20	38,5%
	No	32	61,5%
Diabetes	Yes	12	23,1%
	No	40	76,9%
Hypercholesterolemia	Yes	20	38,5%
	No	32	61,5%

CAD: Coronary Artery Disease

Table 2: Clinical characteristics of autopsy cases.

Specimen preparation

The thoracic aorta was investigated from the commencement of the left ventricle to the level of the diaphragm. After removal from the corpse the aortas were opened longitudinally, photographed, and the interiors were macroscopically examined for fatty streak, raised lesion, plaque, and thrombus (Figure 1). Aortic tissues were carefully excised perpendicular to the long axis from three anatomic stations (Figure 2): 2.5 cm above the aortic valve (Ascending Aorta), 1 cm before the branching of brachiocephalic trunk (Aortic Arch) and 2 cm below the left subclavian artery (Descending Aorta). The choice of these stations was due to sudden changes in direction of the flow and vessel diameter, where blood flow is likely to be disturbed by the formation of secondary and recirculation flows, and endothelial cells are exposed to relatively low shear stress. Thus, they are considered to be preferred sites of atherosclerotic lesions according to literature [12].

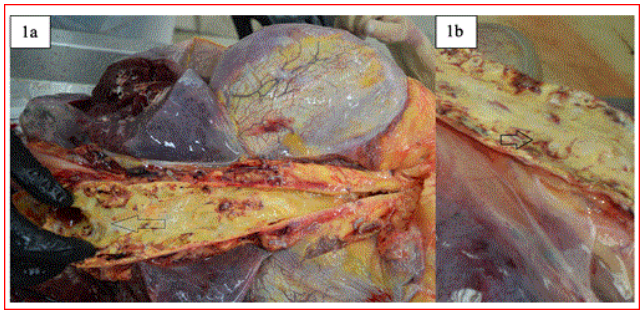

Figure 1: (a) Anatomic sample of the anterior wall 1 cm before the branching of brachiocephalic trunk. (b) Anatomic sample of the descending aorta 2 cm below the left subclavian artery.

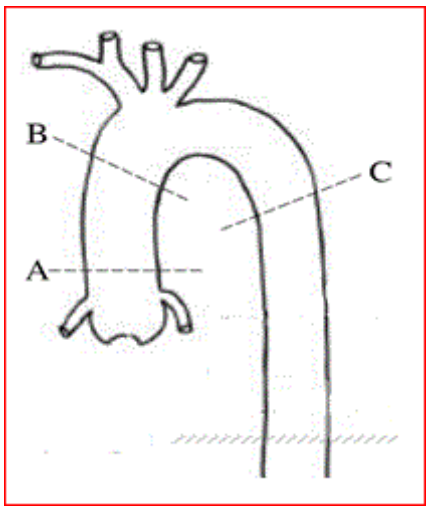

Figure 2: Schematic illustration of the sites of specimen collection. A: Ascending aorta; B: Aortic arch; C: Descending aorta.

Histopathological examination

Five mm-thick paraffin sections perpendicular to the long axis of the vessel were prepared and stained with hematoxylin and eosin for general examination. Each stained section was examined regarding the extend of the atheromatic invasion to the vessel wall: No atherosclerosis, Intima, Media. Sections were then histopathologically graded for scoring: 0 (intact histology), 1 (initial lesion-isolated macrophage, foam cells), 2 (fatty streak-intracellular lipid accumulation), 3 (intermediate lesion-grade 2+small extracellular lipid pools), 4 (atheroma-grade 2+core of extracellular lipid), 5 (fibroatheroma-lipid core and fibrotic layer, or multiple lipid cores and fibrotic layers, or mainly calcific, or mainly fibrotic), and 6 (complicated lesion-surface defect, hematoma-hemorrhage, and thrombus), according to the criteria adopted from a previous study [13]. A further immunohistochemical examination was performed using Tyrosine Hydroxylase (TH) F-11 monoclonal antibody (Santa Cruz Biotechnology Inc., Dallas, Texas, USA) for determining the presence of neuron terminals onto the aortic wall of each section (Figure 3).

The extend of the atherosclerotic lesion, age, ATHERO score and the number of neuron terminals were compared between each segment of the same subject, and between numbers of segments with atherosclerotic change of different subjects. Age, gender, smoking, hypertension, CAD, diabetes and HC were also considered for comparison between all subjects.

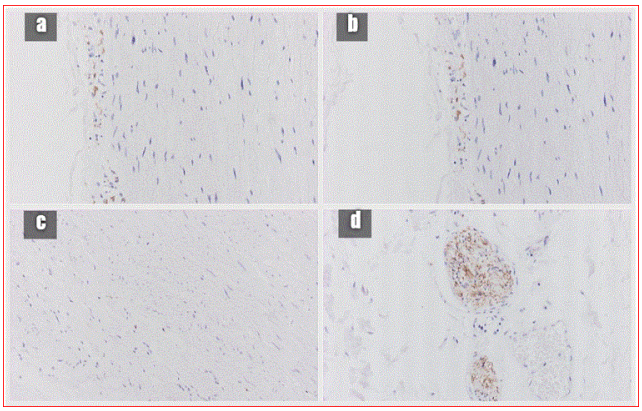

Figure 3: Representative images of immunohistochemical investigation for the presence of TH nerve terminals in aortic wall. Many dispersed TH positive nerve fibers are found at the outer portion of the wall in sections of ascending (a) and descending (b) aorta. Few positive fibers near the vessels in a specimen of aortic arch are observed in (c). Nerves were used as positive control (d). (a-d: immunohistochemistry x200).

Statistical analysis

Data were analyzed with the SPSS (SPSS Inc, Chicago, Illinois, USA) for Mac OS statistical software. The results of analyses of the continuous variables are given as mean ± SD. Data between each segment and between numbers of segments with atherosclerotic change and age were compared by ANOVA. Differences were considered significant if p values were less than .05. For determination of the relationship between ATHERO score and presence of neuron terminals, Pearson correlation coefficients were computed and multiple regression analyses were done.

Results

Clinical characteristics by age

As shown in Table 3 clinical characteristics were not significantly different between age groups (<65 yrs->65 yrs), except for hypertension. There were 26 subjects in each group, with men predominating in both groups (p=.129), Smoking (p=.429), CAD (p=.169), Diabetes (p=.081) and HC (p=.119) were the clinical characteristics with no statistical significance between the two age groups.

However, in the current study 10 subjects aged<65 years and 19 subjects aged>65 years had a positive history of hypertension, with a significant positive correlation (r=.450, p=.023). Moreover, both the prevalence and severity of aortic atheromas (ATHERO Score>4) were significantly influenced by age, with a strong positive correlation between all three segments of the aorta and the two age groups (<65 years>65 years). As shown in Figure 4 the presence of atheromas were common in all subjects regardless of age and segment, with atherosclerosis increasing by age; Ascending aorta (r=.571, p<.001), Aortic arch (r=.655, p<.001), Descending aorta (r=.659, p<.001).

	Age group		
	<65 (n=26)	**>65 (n=26)**	**p Value**
Male/Female	18-Aug	20-Jun	0.129
Smoking	19	16	0.429
Hypertension	10	19	.023*
CAD	7	13	0.169
Diabetes	4	8	0.081
HC	10	10	0.119
CAD: Coronary Artery Disease; HC: Hypercholesterolemia. *Statistical significance p<.05			

Table 3: Clinical characteristics in study subjects by age.

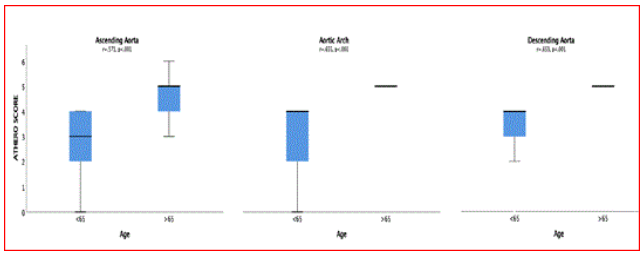

Figure 4: Changes of the atherosclerosis score in the three segments related with age. Statistical significance p<.05.

Clinical characteristics by extend of atheroma and presence of neuron terminals

A total of 96.2% of all subjects had atherosclerotic changes of variable degree in one or more segments; intact histology in all segments was extremely rare. The clinical characteristics of all subjects related to the extent of the atheromatic lesion and the presence of neuron terminals in each segment of the aorta are summarized in (Tables 4a-4c) representing the ascending aorta, the aortic arch and the descending aorta respectively.

Regarding the ascending aorta (Table 4a), hypertension had a significant positive relation with both the extent of the lesion and the presence of neuron terminals onto the aortic wall. By microscopic examination, 6 subjects with a history of hypertension had no atherosclerosis, 6 had intima invasion and 17 had invasion of the media. In addition, 6 subjects with hypertension had no neurons in their ascending aortic wall, 15 had few neurons noted and 8 had many neurons (r=.637, p=.037). Similar findings were also observed in the aortic arch specimens (Table 4b).

Hypertension had a significant positive relation with both the extend of the lesion and the presence of neuron terminals onto the aortic wall. 2 subjects had no atherosclerosis observed, 2 had intima invasion and 25 had media invasion. Regarding the presence of neuron terminals, 8 subjects had no neurons detected, 13 had few and 8 had many neurons (r=.431, p=.046).

As for the descending aorta (Table 4c), hypertension had also a significant positive relation. All of the subjects with hypertension had a degree of wall invasion; 3 into the intima and 26 into the media. 7 subjects had no neurons noted, 12 had few neurons and 10 subjects had many neurons onto the aortic wall (r=.611, p=.045).

In addition, male gender was also found to have a statistical significance regarding the extent of the lesion and the presence of neuron terminals in the descending aorta (p=.033). Age, Smoking CAD, Diabetes and HC, on the other hand, had no significance whatsoever regarding all three segments of the thoracic aorta.

		Ascending aorta						
		Extend of lesion			Neuron terminals			
		No atherosclesosis	Intima	Media	No neurons	Few neurons	Many neurons	p Value
Age	<65	6	6	14	8	12	6	0.406
	>65	5	7	14	4	14	8	
Gender	Male	9	7	22	9	20	9	0.819
	Female	2	6	6	3	6	5	
Smoking		8	7	20	11	17	7	0.062
Hypertension		6	6	17	6	15	8	.037*
CAD		4	3	13	6	8	6	0.427
Diabetes		4	1	7	3	5	4	0.929
HC		7	4	9	3	12	5	0.13
CAD: Coronary Artery Disease; HC: Hypercholesterolemia, *Statistical significance p<.05								

Table 4a: Clinical characteristics in study subjects by extend of lesion and presence of neuron terminals.

		Aortic arch						
		Extend of lesion			Neuron terminals			
		No atherosclesosis	Intima	Media	No neurons	Few neurons	Many neurons	p Value
Age	<65	4	5	17	6	9	11	0.312
	>65	1	4	21	7	15	4	
Gender	Male	4	8	26	8	18	12	0.431
	Female	1	1	12	5	6	3	
Smoking		4	6	25	10	15	10	0.67
Hypertension		2	2	25	8	13	8	.046*
CAD		2	1	17	7	7	6	0.175
Diabetes		3	1	8	3	8	1	0.398
HC		2	3	15	6	8	6	0.141
CAD: Coronary Artery Disease; HC: Hypercholesterolemia. *Statistical significance p<.05								

Table 4b: Clinical characteristics in study subjects by extend of lesion and presence of neuron terminals.

		Descending aorta						
		Extend of lesion			Neuron terminals			
		No atherosclesosis	Intima	Media	No neurons	Few neurons	Many neurons	p Value
Age	<65	3	4	19	6	9	11	0.215
	>65	0	4	22	6	12	8	
Gender	Male	1	6	31	11	17	10	.033*
	Female	2	2	10	1	4	9	
Smoking		2	3	30	10	15	10	0.144

Hypertension		0	3	26	7	12	10	.045*
CAD		0	2	18	7	7	6	0.223
Diabetes		0	2	10	3	5	4	0.62
HC		0	3	17	5	9	6	0.162
CAD: Coronary Artery Disease; HC: Hypercholesterolemia. *Statistical significance p<.05								

Table 4c: Clinical characteristics in study subjects by extend of lesion and presence of neuron terminals.

Atherosclerotic change related to neuron terminals in each segment

The number of subjects who showed an atherosclerotic change and calcified fibroatheroma according to the segment is summarized in Table 5. Minor atherosclerotic changes (score 1-3) were very rare in all 3 segments. On the other hand, atheroma (score 4) and fibroatheroma (score 5-6) were prevalent throughout the thoracic aortic wall. A total of 61.5% of all subjects had ATHERO Score 4-6 in the ascending aorta, 78.9% in the aortic arch and 86.5% in the descending aorta. Percentages of atherosclerotic changes in the three segments are shown in Figure 5.

The relation of atherosclerotic change with the presence of neuron terminals in each of the three thoracic aortic segments is shown in Figure 6. There was a strong negative correlation between ATHERO Score and the presence of neuron terminals regarding all three segments (Ascending aorta: r=-.246, p=.041; Aortic arch: r=-.400, p=.003; Descending aorta: r=-.234, p=.047).

ATHERO score	Ascending aorta N=52	Aortic arch N=52	Descending aorta N=52
0	2	2	2
1	1	2	0
2	4	3	3
3	13	4	2
4	18	20	23
5	12	17	18
6	2	4	4

Table 5: Number of subjects with atherosclerotic change.

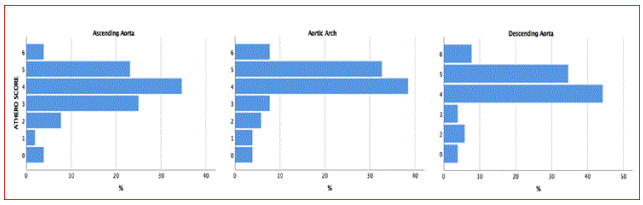

Figure 5: Percentages of subjects with atherosclerotic changes in the three segments.

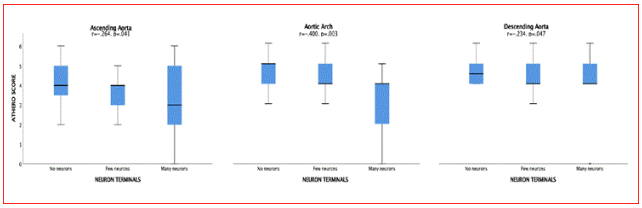

Figure 6: Changes of the atherosclerosis score in the three segments related with the presence of neuron terminals. Statistical significance p<.05.

Discussion

The study results reveal that:

1. Progressive atherosclerosis of the thoracic aorta is common in adults of all ages;

2. Hypertension can affect the ANS neurotransmission onto sites of the thoracic aorta, especially when well organized atheromas are present and

3. The effect of ANS to the thoracic aorta is impaired by the presence of atherosclerosis.

Atherosclerosis is an inflammation process of large and medium sized arteries, characterized by progressive thickening of the intima of the vessel wall, resulting in its eventual hardening [14]. In human beings, atherosclerosis is the most common pathologic process leading to CVD [15-17]. Many studies have demonstrated that atherosclerotic changes of an arterial wall in humans occur not randomly, and not everywhere in the arterial tree, but preferably at certain sites such as the inner wall of curved segments and outer walls of bifurcations of relatively large arteries (i.e., thoracic aorta) [18-21].

Aortic diseases, therefore, are diverse, and are associated with multiple biological systems in the aortic wall, and their interaction with blood flow. The prevalence of aortic diseases varies along the aorta, including the ascending aorta, aortic arch, descending aorta, and abdominal aorta. In a study by Allaire et al. atherosclerotic aneurysms were found to be at least three times more frequent in the abdominal aorta than in the descending thoracic aorta [22]. In contrast, 65% of cases of aortic dissection occur in the ascending aorta, with 20% in the descending aorta, 10% in the aortic arch, and only 5% in the abdominal aorta [23]. This can be attributed to differences in the biological architecture of the aorta, particularly to the perfusion system of the aortic wall. In the current study no aneurismal change was found after explanation of the thoracic aorta, despite the fact that the

preferred sites of examination, as described in the Methods section, were prone to the accumulation of aneurismal changes or dissection.

Nonetheless, atherosclerosis was found to be common in all subjects regardless of age. It is known that the formation of atheromas is an ongoing process, beginning from early childhood. In the study by Allison et al. both the prevalence and severity of aortic atheromas were significantly influenced by age: at age under 50 yrs the prevalence of calcification was 16% and increased to 93% by age over 70 years [24,25]. It has also been stated by similar studies that the development of atherosclerosis increases markedly with age up to an age of about 65, regardless of sex and ethnic background [26,27]. These results come to an agreement with the present study's findings. As depicted in Figure 3, no subject under the age of 65 had scored>4 for ATHERO, and all subjects>65 years scored ATHERO>4 for all three segments. Moreover, a total of 61.5% of all subjects had ATHERO Score 4-6 in the ascending aorta, 78.9% in the aortic arch and 86.5% in the descending aorta respectively.

Data from pathology Transesophageal Echocardiography (TEE), and, more recently, scanning and magnetic resonance imaging studies have shown that atherosclerotic disease of the aortic arch is an independent risk factor for recurrent vascular events. Thoracic aorta atherosclerosis is also a powerful marker for generalized atherosclerosis (coronary, carotid, and peripheral arterial disease, including aneurysms). Among vascular risk factors, hypertension, smoking and HC are associated with severe plaques in the thoracic aorta [28-31]. The role of the Sympathetic Nervous System (SNS) in the pathogenesis of Hypertension (HT) has been remarkably changed over the past 50 years, thanks to the development of methodological approaches allowing direct assessment of systemic and regional sympathetic cardiovascular drive in humans [32-34]. The relationships between endothelial dysfunction and ANS imbalance imply a close interrelationship between the endothelium and ANS. Autonomic cardiovascular control is impaired in hypertension, leading to a reduction in the parasympathetic tone and an increase in the sympathetic influences to the heart and peripheral vessels. Cardiac output and systemic vascular resistance are the major effector components of neural blood pressure regulation [35]. Gamboa et al. indicated that in the setting of pathologic conditions such as hypertension, the interrelationship between the ANS and vascular function may contribute to the pathologic process [36].

However, studies in patients with hypertension and high sympathetic tone shows that the increased risk of coronary artery disease cannot be fully attributed to blood pressure elevation alone [37], also suggesting other links between ANS modulation and CVD, one of them being inflammation [38]. The concept of inflammation is central in atherosclerosis, and suggested to provide a mechanistic link between some of the traditional risk factors, such as hypertension, and the progression of atherosclerosis [39]. Previous studies have reported that autonomic dysfunction associates with both atherosclerosis and CVD [40-42]. Surprisingly, few studies have investigated if autonomic dysfunction is directly related to CVD, or if hypertension could mediate this association, and to our knowledge, never with thoracic aorta atherosclerosis as the primary endpoint.

In the current study, hypertension is a major risk factor that clearly affects both the extend of atheromatic lesions and the presence of ANS in the three segments of the thoracic aorta. This fact could possibly be attributed to stress-induced hypertension. Mental stress is a powerful stimulus for central sympathetic excitation [43]. Ghiadoni et al. reported that acute mental stress induced transient endothelial dysfunction, lasting up to 4 h, accompanied by blood pressure, heart rate, and salivary cortisol increases [44]. The effects of psychosocial stress have also been investigated in animal models, showing accelerated atherosclerosis in cynomolgus monkeys and mice living in an unstable environment [45-47]. Studies have investigated the effects of targeting this route with pharmacological interventions. Inhibition of sympathetic drive using treatment with β-adrenergic antagonists (β-blockers), such as metoprolol, reduces mortality in patients with hypertension and heart failure [48,49]. Further, upregulation of the SNS in psychosocial stress is reported to be associated with increased proliferation of neutrophils and inflammatory monocytes in mice and humans [50,51]. Such evidence provided by previous studies as well as this paper suggest that psychosomatic factors may contribute to the development of atherosclerosis, and that there may be an underlying mechanism for the activation of the sympathetic nervous system, which adversely impacts the process of atherosclerosis in thoracic aorta.

However, although the ANS may impact on vascular function, the reverse may also be true. Animal experiments showed that removal of the atherosclerotic endothelium increased the release of norepinephrine from sympathetic nerve terminals in rabbit carotid artery [52]. Draid et al. demonstrated that the adventitia is a site for these autonomic innervations, and it can affect the process of endoluminal atherosclerotic progression via several mechanisms. Consequently, insufficient adaptation of the adventitia may increase the risk of end-organ dysfunctions, including inflammation and atherosclerosis [53]. Such evidence implies an inability of endothelium on ANS in pathological conditions. Sobey et al. reported that endothelial dysfunction damages the sympathetic activity and decreases the reuptake of norepinephrine into the sympathetic nerves to counteract the vasoconstriction factors in rabbit aorta [54]. These findings come to an agreement with the results of the present study, where the effect of ANS to the thoracic aorta was severely impaired by the presence of atherosclerosis.

Autopsy studies such as this, along with similar clinical and animal studies, provide a mean of understanding the basic process which sets a stage for clinically significant atherosclerotic cardiovascular disease. There is no valid method of sampling of living population. It is, therefore, considered that more necropsy studies, such as this, could probably provide the best sample of the living population for studying atherosclerosis.

However, this study did not take under consideration several aspects that might affect the relationship atherosclerosis and ANS, such as Body Mass Index (BMI) and size of the aorta. The primary aim was the morphologic investigation of this relationship through histopathology, without further studying the innervation of blood vessels by the ANS neurotransmitters in atherosclerosis. These limit a compatible explanation of this study's results.

Conclusion

In conclusion, this findings support that there is a significant two-way relationship between autonomic disfunction and the presence of atherosclerosis in human thoracic aorta in adults of all ages, especially when hypertension is present. It is therefore possible that stress-induced hypertension can be considered as a potential risk factor for the development of atherosclerosis. Large scale studies, therefore, are needed to confirm the relationship between the ANS and the development of atherosclerosis in humans that still remains elusive.

Authors' Contributions

AG made a thorough literature research and was the chief author in terms of building the paper. TK conducted the histopathological examination of the specimens. LP, DP and TR assisted with the linguistics and performed literature research. AL assisted with the statistical analysis. NB and FC gave their specialist advice on scientific issues of the paper. FC checked the final version of the manuscript. All authors have read and approved the final manuscript.

Footnote

The manuscript is not under consideration and has not been published by any other journal. The authors declare no conflict of interest. This study was carried out in accordance with the World Medical Association's Declaration of Helsinki.

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