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Sympathetic Hyperactivity and Aortic Sympathetic Nerve Sprouting in Patients with Thoracic Aortic Dissection

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Background: To determine the yet unknown relation between thoracic aortic dissection (TAD) and sympathetic nervous system activity.
Methods: Variables such as electrocardiography, blood pressure, respiratory activity, postganglionic muscle sympathetic nerve activity (MSNA) , plasma norepinephrine, tyrosine hydroxylase−positive nerve fiber density, and growth-associated protein 43−positive nerve fiber density were detected and statistically analyzed.
Results: TAD Patients showed a significant lower R-R interval variance and higher blood pressure, heart rate, respiratory rate, MSNA, plasma norepinephrine (reflecting elevated sympathetic nervous system [SNS] activity), higher tyrosine hydroxylase, growth-associated protein 43−positive nerve fiber density (reflecting sympathetic sprouting and innervation) than those of the control group.
Conclusions: In TAD patients, both overall and regional aortic SNS activities are elevated.

INTRODUCTION

Thoracic aortic dissection (TAD) is a highly lethal vascular disease. In many patients with TAD, the aorta progressively dilates and ultimately ruptures.[1] Several risk factors contributing to TAD, such as cocaine abuse, hypertension, sleep apnea syndrome, and pregnancy,[2,3] are all in company with sympathetic hyperactivity. This raises a possibility that sympathetic nervous system (SNS) activity abnormity also contributes to TAD formation.

Cystic medial degeneration, a key feature of TAD, is typically accompanied by elastic fiber fragmentation, loss of smooth muscle cells (SMCs), and accumulation of amorphous extracellular matrix (ECM) in the aortic wall.[4−6] Other diseases such as myocardial hypertrophy after congestive heart failure, hypertrophic cardiomyopathy, and ulcerative colitis also experienced pathologic changes of SMC, ECM, and elastic fiber. Especially, these pathologic changes could be regulated by autonomic nervous system activity.[7−9] Such studies hint us that SNS activity may be a regulator of both functional and structural properties of the aorta, and furthermore, SNS activity abnormity may affect the pathologic changes of TAD. This possibility has been partly proven by further study. Thoracic sympathectomy, simulating a regional SNS activity reduction, induces structural and biomechanical remodeling of the thoracic aorta.[10] But whether SNS activity is abnormal in TAD is still unclear.

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This study was, therefore, designed to determine the yet unknown relation between TAD and SNS activity.

MATERIALS AND METHODS

Subjects

The study protocol was approved by the Medical Ethics Committee of the Renmin Hospital of Wuhan University, and informed consent was obtained from each subject.

For comparison 1, 27 patients with TAD (19 men and 8 women) without phenotypic characteristics of any of the known genetic disorders, such as Marfan's syndrome, were included in the experimental group for detecting overall SNS activity. Control experiments were performed in 14 healthy people (7 men and 7 women), who volunteered to participate in this study. None of the people in the control group was diagnosed for the following diseases or experienced such disease history: hypertension, autonomic nervous functional disorder, rheumatoid diseases, myocardial hypertrophy after any disease, hypertrophic cardiomyopathy, any drug abuse, and sleep apnea syndrome.

For comparison 2, full-thickness aortic wall specimens from 19 patients with TAD (14 men and 5 women) in the experiment group of comparison 1 (8 patients with TAD accepted operations without aortic wall resection, so no aorta sample could be obtained from them. Their aorta wall was used to wrap artificial vascular graft and prevent angiorrhea) were obtained and immediately placed in 4% paraformaldehyde for 18−24 hrs. These specimens were then embedded in paraffin, sliced perpendicular to the longitudinal axis of the aorta, and then subjected to H&E or immunohistochemical staining. Abdominal aortic wall specimens from 5 kidney donors (5 men) and 8 thoracic aortic wall specimens from patients (4 men and 4 women) accepted aortic valve replacement surgery were obtained in the control group.

Recorded Variables

In every subject, electrocardiography, blood pressure, respiratory activity, and postganglionic muscle sympathetic nerve activity (MSNA) were continuously recorded. MSNA was recorded according to the method reported by Furlan et al.[6]

Plasma Norepinephrine Measurement

Venous blood samples for norepinephrine (NE) analysis were collected in ethylene glycol bis(2-aminoethyl) tetraacetic acid tubes 30 min after the patients and volunteers woke up in the morning in the recumbent position. Samples were processed immediately in a refrigerated centrifuge. The plasma was stored at −80°C until analysis. Plasma NE was assayed by high-pressure liquid chromatography with electrochemical detection.[11]

Table I. Baseline data of study population

	TAD ($n = 27$)	CTL ($n = 14$)	P value
Male (n)	19	7	0.4315
Female (n)	8	7	0.4315
Age (years)	41 ± 12.66	35 ± 6.18	0.0415
Weight (kg)	71 ± 26.44	63 ± 14.56	0.5327
BMI (kg/m^2)	30±2*	26 ± 1	<0.0001
Hypertension (n)	2*	0	<0.0001
Medication (n)			
β-Blocker	25*	0	<0.0001
ACEI	4	0	0.0183
Nitrate	25*	0	<0.0001

ACEI, angiotensin-converting enzyme inhibitor; CTL, control group.
Values are given as mean ± standard deviation.
*$P < 0.01$.

Immunohistochemistry

The samples were immunostained for tyrosine hydroxylase (TH, a marker of sympathetic nerve) and for growth-associated protein 43 (GAP43, a marker of active nerve sprouting). Details of the staining techniques have been published previously. Nerve densities were determined by Image-Pro Plus 6.0. Each slide was examined under a microscope to select 3 fields randomly. Nerve density is expressed as the nerve area divided by the total area examined (μm^2/mm^2). The mean density of nerves in these 3 selected fields was used to represent the nerve density of that slide.[12,13]

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation. The data were analyzed by an unpaired Student's t-test to determine intergroup differences. Data were analyzed by SPSS 13.0 software. Statistical significance was defined as $P < 0.01$.

RESULTS

Comparison 1: Overall SNS Activity

Study Population. Baseline data of the study population in comparison 1 are given in Table I. The TAD group had higher average body mass index (BMI) and higher incidence of hypertension than the