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Endoscopic Thoracic Sympathectomy in the Treatment of Vasospastic Angina Resistant to Medical Therapy

ABSTRACT

Background: In this study, we aimed to investigate the clinical follow-up results of endoscopic thoracic sympathectomy (ETS) in the treatment of vasospastic angina (VSA) resistant to maximal medical therapy.

Methods: A total of 80 patients with VSA who presented to our hospital between 2010 and 2022 were included in our study. Among them, 6 patients who did not respond to medical therapy underwent ETS. In-hospital and long-term clinical outcomes of patients who underwent ETS were recorded.

Results: The median age of the patients with VSA was 57 [48-66] years, and 70% of the group were males. In the ETS group, compared to the non-ETS group, higher numbers of hospital admissions and coronary angiographies were observed before ETS (median 6 [5-6] versus 2 [1-3], $P < .001$; median 5 [3-6] versus 2 [1-3], $P = .004$, respectively). Additionally, while 2 patients (33.3%) in the ETS group had implantable cardioverter defibrillator (ICD), only 2 patients (2.7%) in the non-ETS group had ICD ($P = .027$). Out of the 6 patients who underwent ETS, 2 were females, with a median age of 56 [45-63] years. Four patients underwent successful bilateral ETS, while 2 patients underwent unilateral ETS. During the follow-up period after ETS, only 3 patients experienced sporadic attacks (once in 28 months, twice in 41 months, and once in 9 years, respectively), while no attacks were observed in 3 patients during their median follow-up of 7 years.

Conclusion: It appears that ETS is effective in preventing VSA attacks without any major complications.

Keywords: Vasospastic angina, endoscopic thoracic sympathectomy, cardiac sympathetic denervation

ORIGINAL INVESTIGATION

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INTRODUCTION

Vasospastic angina (VSA) is an important cardiac disorder that can lead to various clinical scenarios such as stable angina, sudden cardiac death, acute coronary syndrome, arrhythmia, or syncope.[1-3] Vasospastic angina accounts for 3-11% of out-of-hospital cardiac arrest cases.[4,5] It was initially described by Prinzmetal[6] and his colleagues in 1959 as a variant form of angina characterized by transient ischemic electrocardiographic (ECG) changes during rest and preserved exercise capacity. The mechanism of coronary spasm has not been fully elucidated, and multiple factors have been implicated.[7-12] Activation of sympathetic nervous system is considered to be an important contributing factor.[13,14] In the treatment of VSA, nitrates and calcium channel blockers are primarily utilized. An implantable cardioverter defibrillator (ICD) can be employed for secondary prevention in patients who develop malignant arrhythmias. Medical treatment responders have a good prognosis, but this is not the case for refractory patients (patients symptomatic despite maximally tolerated therapy), and uncertainties regarding management persist. There is limited information in the literature regarding the treatment of medically refractory cases with cardiac sympathetic denervation. This procedure was initially performed as an accompanying method to open surgery in the past, but nowadays, it can be carried out minimally invasively with endoscopic thoracic

sympathectomy (ETS).[15-17] However, apart from case series, there is a lack of studies on this subject.[18-20]

In this study, our aim was to provide the clinical follow-up results of the patients who underwent ETS in the treatment of medically refractory VSA.

METHODS

A total of 80 patients diagnosed with VSA in our hospital between 2010 and 2022 were retrospectively included in this study. Clinical and laboratory parameters of the patients were obtained from medical records. All patients underwent coronary angiography. Angiographic images of the patients were interpreted by at least 2 experienced interventional cardiologists at our institution. Among them, 6 patients who did not respond to medical therapy underwent ETS. In-hospital and long-term clinical outcomes of patients who underwent ETS were recorded. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the Local Ethics Committee approved the study protocol.

HIGHLIGHTS

- Vasospastic angina (VSA) is an important cardiac disorder that can lead to various clinical scenarios.
- This disorder is relatively rare and generally has a good prognosis with medical treatment.
- It can lead to life-threatening arrhythmias, acute coronary syndrome, and death, especially in patients refractory to medical therapy.
- In the present study, endoscopic thoracic sympathectomy effectively reduced VSA attacks in patients resistant to medical treatment.

Vasospastic Angina

Vasospastic angina was defined as a nitrate-responsive angina during a spontaneous episode (rest angina, especially between night and early morning), which may or may not be associated with ECG changes (transient ST-segment elevation of ≥ 0.1 mV, ST-segment depression of ≥ 0.1 mV, or new appearance of negative U waves in at least 2 contiguous leads on the 12-lead ECG), can be demonstrated with coronary angiography showing coronary vasospasm during spontaneous angina and its resolution with nitrate administration (critical stenosis defined as ≥70% and resolution defined as a decrease of stenosis to <50%).[21,22]

Endoscopic Thoracic Sympathectomy

Prior to the operation, all patients were informed about the surgical technique, expected benefits, and potential risks, and their consent was obtained. The operation was conducted under general anesthesia for all patients. A 5 mm thoracic port was inserted at the fourth or fifth intercostal space along the axillary line, and the procedure continued based on the lung adhesions. In bilateral applications, the chain was terminated by using cautery to burn the third and fourth sympathetic ganglia, first on the right side and then on the left side. The effect on heart rhythm was observed after burning the right side. If no bradycardia/arrhythmia occurred, the left side was also blocked. After the placement of drains, the operation was concluded. Once full lung expansion was achieved postoperatively, the drains were removed, and the patient was discharged.

Statistical Analyses

Statistical analyses were conducted using R version 4.3 (R Foundation for Statistical Computing, Vienna, Austria) with the "desktool" package. Shapiro–Wilk test and visual

Table 1. Baseline Demographic and Laboratory Characteristics of the Study Group

	All Patients (n = 80)	ETS Group (n = 6)	Non-ETS Group (n = 74)	*P*
Age (years)	57 [48-66]	56 [45-63]	57 [48-66]	.677
Sex (male)	56 (70)	4 (66.7)	52 (70.3)	.853
Diabetes mellitus	8 (10)	–	8 (10.8)	.396
Hypertension	36 (45)	2 (33.3)	34 (45.9)	.550
Smoking	38 (47.5)	4 (66.7)	34 (45.9)	.328
Drug abuse	2 (2.5)	1 (16.7)	1 (1.4)	.144
Ejection fraction (%)	60 [55-60]	60 [60-60]	60 [54-60]	.333
Hemoglobin (g/dL)	13.1 [12.6-14.1]	13.9 [11.7-13.9]	13.1 [12.7-14.2]	.689
Creatinine (mg/dL)	0.9 [0.7-0.99]	0.8 [0.75-0.90]	0.9 [0.7-1]	.725
LDL-chol (mg/dL)	91 [65-121]	72 [61-86]	94 [66-122]	.271
Previous medication				
Nitrate	57 (81.4)	6 (100)	51 (75)	.153
CCB	53 (66.2)	6 (100)	47 (69)	.170
Clopidogrel	38 (47.5)	3 (50)	35 (50.7)	.973
ASA	66 (82.5)	4 (66.7)	62 (91.2)	.124
Beta-blocker	19 (23.7)	–	19 (27.9)	.328
ACEI/ARB	33 (41.2)	2 (33.3)	31 (45.6)	.683

Categorical data are presented as numbers (percentages), and continuous data are presented as median [interquartile range].
ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ASA, acetylsalicylic acid; CCB, calcium channel blocker; ETS, endoscopic thoracic sympathectomy; LDL-chol, low-density lipoprotein cholesterol.

histograms were used to assess the distribution of the variables. Continuous variables were presented as median [interquartile range], while categorical variables were reported as counts and percentages. Mann–Whitney *U*-test was employed to compare medians while Fisher's exact test was used to analyze categorical variables. Two-tailed $P < .05$ was considered statistically significant.

RESULTS

In our study, the median age of the 80 patients presenting with VSA was 57 [48-66] years, and 70% of them were males. Among them, 6 patients who experienced VSA attacks resistant to medical treatment underwent ETS. Table 1 provides baseline demographic and laboratory characteristics of the patients. There was no significant difference between ETS and non-ETS groups in terms of age, gender, and prevalences of hypertension, diabetes mellitus, and smoking. Prior medication, left ventricular ejection fraction, and laboratory parameters were similar among groups. Additionally, previous cannabis use was present in both groups.

Clinical characteristics of ETS and non-ETS groups before operation are depicted in Table 2. Compared to non-ETS group, higher numbers of hospitalizations (number of documented attacks) and coronary angiographies were observed in ETS group before the procedure (median 6 [5-6] versus 2 [1-3], $P < .001$; median 5 [3-6] versus 2 [1-3], $P = .004$; respectively). The histograms of the number of coronary angiographies before ETS in all patients and 2 groups are illustrated in Figure 1. Furthermore, while 33.3% of the patients in the ETS group had ICD, this rate was only 2.7% in the non-ETS group ($P = .027$).

The characteristics of the patients refractory to medical treatment and underwent ETS are presented in detail in Table 3. The median age of the ETS group was 56 [45-63] years and 2 of them were females. Among these patients, 1 had recurrent ST-segment elevation myocardial infarctions (STEMI), 2 had non-ST-segment elevation myocardial infarction (NSTEMI), and 3 had both STEMI and NSTEMI as clinical presentations. Additionally, 2 patients presented with malignant arrhythmias, and ICDs were implanted to these patients. Four patients had vasospasm in a single coronary artery (mostly in right coronary artery), and 2 patients had vasospasm in all 3 major coronary arteries. All patients were symptomatic despite treatment with maximally tolerated doses of nitrates and calcium channel blockers. Thus,

Table 2. Clinical Characteristics of the Groups Before Endoscopic Thoracic Sympathectomy

	All Patients (n = 80)	ETS Group (n = 6)	Non-ETS Group (n = 74)	*P*
Pre-op hospitalization				<.001
Median [IQR]	2 [1-4]	6 [5-6]	2 [1-3]	
Mean	2.79	5.83	2.54	
Pre-op coronary angiographies				.004
Median [IQR]	2 [1-3]	5 [3-6]	2 [1-3]	
Mean	2.44	4.67	2.26	
Stent present	23 (29)	–	23 (31)	.010
Number of stents				.113
Median [IQR]	0 [0-1]	–	0 [0-1]	
Mean	0.54	–	0.58	
ICD implantation	4 (5)	2 (33.3)	2 (2.7)	.027
Diagnosis at admission				.458
USAP	8 (10)	–	8 (10.8)	
NSTEMI	36 (45)	2 (33.3)	34 (45.9)	
STEMI	36 (46)	4 (66.7)	32 (43.2)	
Vasospastic vessel				.748
LAD	28 (35)	1 (16.7)	27 (36.5)	
CX	4 (5)	–	4 (5.4)	
RCA	29 (36.3)	3 (50)	26 (35.1)	
LAD+CX	4 (5)	–	4 (5.4)	
LAD+RCA	2 (2.5)	–	2 (2.7)	
RCA+CX	1 (1.3)	–	1 (1.4)	
LMCA	2 (2.5)	–	2 (2.7)	
Three-vessel	10 (12.5)	2 (33.3)	8 (10.8)	

Categorical data are presented as numbers (percentages), and continuous data are presented as median [interquartile range].
CX, circumflex artery; ETS, endoscopic thoracic sympathectomy; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LAD, left anterior descending artery; LMCA, left main coronary artery; NSTEMI, non-ST-segment elevation myocardial infarction; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction; USAP, unstable angina pectoris.

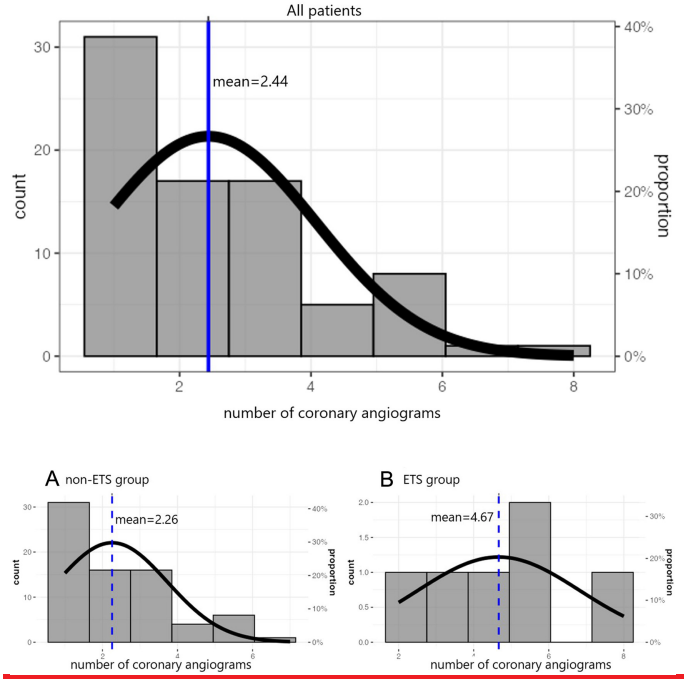

Figure 1. Histograms presenting the coronary angiography rates of the patients. Histogram at the top of the figure shows the number of coronary angiograms in all the study groups. Below, there are 2 histograms demonstrating the coronary angiography rates of non-ETS (A) and ETS group (B) separately. ETS, endoscopic thoracic sympathectomy.

Table 3. Demographic and Clinical Characteristics and Follow-Up of the Endoscopic Thoracic Sympathectomy Group

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	66	59	42	53	41	64
Gender	Male	Male	Female	Male	Female	Male
Diabetes mellitus	+	–	–	–	–	–
Hypertension	+	–	–	+	–	–
Smoking	–	+	–	+	–	+
Drug abuse	–	+	–	–	–	–
EF (%)	45	55	60	60	60	55
Diagnosis at admission	STEMI	STEMI	STEMI	NSTEMI	NSTEMI	STEMI
Vasospastic vessel	LAD/RCA/CX	RCA	RCA	LAD	LAD/RCA/CX	RCA
Medications used	Nitrate CCB ASA Clopidogrel Statin	Nitrate CCB ASA Clopidogrel Statin ACEI/ARB	Nitrate CCB Clopidogrel Ranolazin	Nitrate CCB ASA Statin ACEI/ARB	Nitrate CCB	Nitrate CCB ASA
ICD implantation	–	–	+	–	+	–
Preprocedural hospital admissions	6 times	5 times	5 times	5 times	8 times	6 times
Pre-ETS follow-up	8 years	2 years	1.6 years	3 years	4 years	2 years
Recurring STEMI	1	5	3	–	–	4
Recurring NSTEMI	5	–	1	5	7	2
VT/VF	–	–	1	–	1	–
ETS type	Unilateral	Unilateral	Bilateral	Bilateral	Bilateral	Bilateral
Postprocedural hospital admissions	1 time	–	2 times	–	1 time	–
Post-ETS follow-up	28 months	29 months	41 months	122 months	108 months	84 months

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ASA, acetylsalicylic acid; CCB, calcium channel blocker; CX, circumflex artery; EF, ejection fraction; ETS, endoscopic thoracic sympathectomy; ICD, implantable cardioverter defibrillator; LAD, left anterior descending artery; NSTEMI, non-ST-segment elevation myocardial infarction; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction; VT/VF, ventricular tachycardia/ventricular fibrillation.

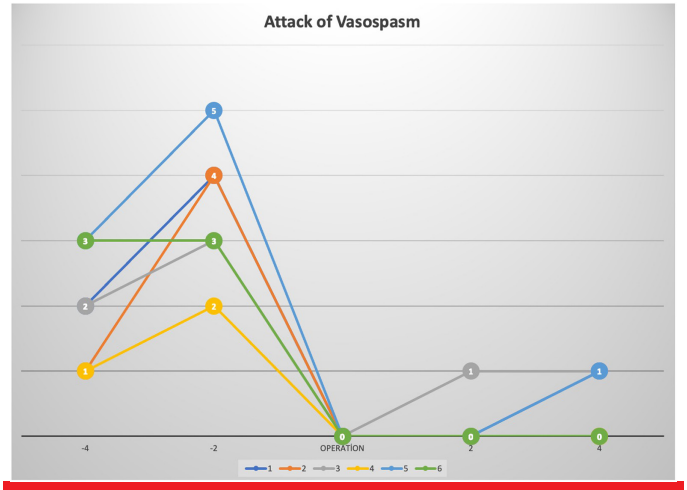

Figure 2. Frequencies of vasospastic angina attacks during the follow-up period before and after endoscopic thoracic sympathectomy (ETS) for each patient in the ETS group. Each patient is denoted with a different color. Numbers denoting the patients are the same as in Table 3.

successful bilateral ETS was performed in 4 patients and unilateral ETS in 2 patients. None of the patients experienced any complications. During the follow-up period after ETS, 3 patients had VSA attacks, but the frequency of these attacks was significantly lower than before ETS. No attacks were observed in 3 patients during a median follow-up of 7 years (Figure 2).

DISCUSSION

This study demonstrated that ETS was effective in preventing VSA attacks in patients resistant to medical treatment without any complications.

Coronary spasm is a heterogeneous phenomenon that may occur in patients with or without coronary atherosclerosis, may be focal or diffuse, and may affect epicardial or microvascular coronary arteries.[23] The exact incidence of VSA is unknown due to factors such as underdiagnosis, infrequent use of provocative tests in diagnosis, and variation in frequency in different populations. In a study by Montone et al,[24] provocative tests were positive in 46.2% of the patients with acute myocardial infarction and nonobstructive coronary

arteries. The incidence of VSA is higher in Asian populations. In a multicenter Japanese study involving 1601 patients with non-ST-segment elevation acute coronary syndrome, 28% of the patients had no culprit lesion, and a high rate of positivity was observed in the provocative tests of these patients with acetylcholine. This study demonstrated a VSA prevalence of 79.2% in nonculprit non-ST-segment elevation acute coronary syndrome patients.[25]

Diagnosis of VSA has been defined by various criteria in the literature.[21,22] In our study, the diagnosis was made based on these criteria. Coronary angiography was performed on all patients, and it demonstrated spontaneous significant narrowing due to vasospasm, which resolved after nitrate administration. The use of provocative tests in the diagnosis is limited to patients with clinical findings suggestive of vasospasm but without critical stenosis on imaging. While there is a high clinical experience with these tests in the Japanese population, they are less commonly performed in many centers due to factors such as patient volume, difficulties in obtaining the necessary substances, and lower sensitivity in young patients and those with resting angina.[25] Calcium channel blockers and long-acting nitrates are the mainstay of the VSA treatment, along with lifestyle changes and control of cardiovascular risk factors.[26] While the prognosis of VSA under medical treatment is generally favorable, it is known that resistant cases can be associated with life-threatening arrhythmias and myocardial infarction.

Although the pathogenesis of coronary artery spasm has not been fully elucidated, different mechanisms have been demonstrated, such as vascular smooth muscle cell hyperreactivity, endothelial dysfunction, magnesium deficiency, low-grade inflammation, oxidative stress, and altered autonomic nervous system response.[7-14] Increased sympathetic tone has been shown to have a role in the pathogenesis and activation of VSA.[13,14] The lower cervical and upper thoracic sympathetic ganglia regulate sympathetic nerve activity to the heart. These ganglia join with vagal fibers to form cardiac plexuses. The main plexuses are located in front of the aorta and trachea and behind the left atrium, near the interatrial septum. Partial sympathetic denervation emerged in the past as an additional treatment method in patients with medically refractory VSA who were candidates for coronary artery bypass grafting. Initially, it was performed as the resection of the entire adventitia along the ascending aorta, known as "plexytomy." Later, it continued as the blockade of a limited number of ganglia in the triangular area between the pulmonary artery, aorta, and trachea.[15-17] The disadvantages of these procedures were their open surgical approach and the limited blockade of ganglia, which resulted in the return of functions. In recent years, case reports and case series have been reported on ETS, which is a more minimally invasive approach in the treatment of refractory VSA.[18-20] Yoshida et al[19] performed bilateral ETS in 5 patients with refractory VSA, and no complications were observed. Symptoms improved in 4 patients, demonstrating the long-term efficacy of ETS in the treatment of refractory VSA. Although there is currently no study specifically on the treatment of recurrent VSA attacks with ETS, its long-term efficacy and safety have been demonstrated. In a study, it was shown that in the long-term follow-up of patients with severe angina pectoris, ETS resulted in a shift in the sympatho-vagal balance toward parasympathetic tone, an increase in global heart rate variability, a decrease in QT dispersion, and consequently a reduction in the risk of malignant arrhythmias and death.[27] Similar to these studies, our study demonstrated that ETS prevented recurrent VSA attacks. Successful ETS was performed on 6 VSA patients with persistent clinical symptoms despite maximally tolerated medical treatment. After sympathectomy, 3 patients had no attacks during a median follow-up of 7 years. In the other 3 patients, quality of life increased with significantly less VSA attacks than before sympathectomy.

Study Limitations

Limitations of the study include its retrospective design and the small number of patients who underwent sympathectomy.

CONCLUSION

Although VSA is relatively rare and generally has a good prognosis with medical treatment, it can lead to life-threatening arrhythmias, acute coronary syndrome, and death, especially in patients refractory to medical therapy. This study showed that ETS can reduce VSA attacks without serious complications and should be kept in mind as a treatment modality in patients who are symptomatic despite maximally tolerated medical treatment. However, comprehensive studies are needed to further investigate the subject.

Ethics Committee Approval: This study was approved by Ethics Committee of Haydarpaşa Numune Training and Research Hospital (approval number: HNEAAH-KAEK/KK/2023/99, date: 22.05.2023).

Informed Consent: Informed consent was not obtained because the retrospective nature of the study and no personnel information was used.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.A.S., G.Z., M.F.Y., T.O., C.Y.K.; Design – M.A.S., G.Z., İ.İ.A., F.C., A.S.; Supervision – M.A.S., A.K., T.O., C.Y.K.; Data Collection and/or Processing – M.A.S., F.C., T.Ç., A.S, O.T., E.Y.; Analysis and/or Interpretation – M.A.S., M.F.Y., F.C., A.S., E.Y., A.K.; Literature Search – M.A.S., G.Z., M.F.Y., İ.İ.A., T.Ç., O.T.; Writing – M.A.S., G.Z., T.Ç., A.S., O.T.; Critical Review – M.A.S., İ.İ.A., E.Y., A.K., T.O., C.Y.K.

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