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Follow-up paper - Thoracic general

Endoscopic thoracic sympathectomy – its effect in the treatment of refractory angina pectoris

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Abstract

Objective: To document an improvement in the quality of life in a group of patients with refractory angina and videothoracoscopic sympathectomy (VTSY) during the early postoperative period and a six-month follow-up. **Methods:** Ten patients with angina CCS IV refractory to a conventional therapy underwent VTSY between the years 1998 and 2002 at our institution. All patients underwent a complex preoperative evaluation, including pain assessment using a visual analog scale (VAS). Proximal thoracic sympathetic blockage was performed in all patients as a diagnostic test. The resection of bilateral Th2-Th4 ganglions was performed under general anesthesia and selective lung ventilation. All patients were monitored 6 months after the VTSY. **Results:** No deaths occurred in our group of patients, with an average hospital stay of 4.1 days. Nine of the ten operated patients referred an important subjective relief of pain. There was a drop from 10 to 4 according to VAS ($P<0.05$), and from 4 to 2.4 according to CCS ($P<0.05$). Decreases in basal heart rate, norepinephrine level, and an occurrence of ventricular premature beats reached the level of statistical significance. **Conclusions:** The increasing number of patients with refractory angina prompted a search for an effective and safe therapy to improve the quality of their life. New evidence in the pathophysiology of an ischemic myocardium and investigation of the impact of thoracic sympathectomy suggests sympathetic denervation seems to be a possible alternative method for the treatment of refractory angina pectoris.

Keywords: Videoscopic thoracic sympathectomy; Refractory angina

1. Introduction

In contrast to recent significant improvements in the treatment of acute and chronic forms of coronary artery disease (pharmacological therapy, PTCA, CABG, mechanical assist device, stem-cell therapy, etc.), the number of patients with coronary artery conditions unsuitable for percutaneous intervention or direct myocardial revascularization is still growing. Gradual progression of atherosclerotic changes over time leads to a further worsening of the quality of life in such patients. The estimated annual incidence of patients with the refractory angina is around 30,000–50,000 in Europe, and 100,000 in the USA [1,2]. The goal of our method is to increase oxygen supply to a diseased myocardium and to relieve angina. Surgical procedures on the autonomous nervous system of the heart have been performed for more than a 100 years. They were originally utilized as palliative procedures to relieve angina in patients with ischemic heart disease. The purpose was to transect the path of the pain from the ischemic myocardium. Transection was performed at the level of sympathetic ganglia. Alexander performed the first cervical sympathectomy in Liverpool in 1889, the same year in which the autonomous nervous system had first been described. Francois Frank proposed cervico-thoracal sympathectomy for angina in 1899, but this procedure was first performed in 1920 by Ionnescu with very good effect. Hyperhidrosis and vasospasms were accepted indications for the use of upper thoracic sympathectomy in this period. An anterior upper-supraclavicular approach was standard for thirty years. Adson and Brown observed good results with a posterior approach in 1929 [3,4]. Hughes performed the first amputation of the sympathetic ganglion via a thoracoscopic approach in 1942. Goetz and Marr from Cape Town first performed a transthoracic approach through the anterior thoracic wall in 1944. Kuks from Innsbruck, who had published more than 1400 operations on sympathetic and splanchnic nerves in 1954, was the pioneer of thoracoscopic surgery [5]. High morbidity and mortality were the limitations for the use of thoracic sympathectomy in

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patients with refractory angina. The use of minimally-invasive surgical techniques dramatically spread the range of effective treatments, so that we are now able to propose sympathectomy even to patients with a high risk to thoracotomy. Minimal postoperative pain and short hospital stay are other important advantages of videothoracoscopic sympathectomy (VTSY). The target of VTSY is to diminish the complaints of a patient, and further, to evaluate the effect of this therapy during a postoperative follow-up period. A wide range of therapeutic possibilities is available nowadays, including transmyocardial laser revascularization [6,7], neuromodulation therapy [8], thoracic epidural analgesia [9,10], left stellate ganglion blockage [11], and therapeutic angiogenesis [12]. The effect of the operation is the cornerstone for the evaluation of the effectiveness of the method. A risk/benefit ratio has to be taken into account for such procedures. There are three potential therapeutic alternatives for patients with refractory angina who are not candidates of PTCA or surgical revascularization according to ACC/AHA 2002 guidelines: transmyocardial laser revascularization (TMLR) in the class II a, and external counter-pulsation [13] and spinal cord stimulation in the class II b [14]. In spite of early improvements in the quality of life of patients receiving such treatment, there is a lack of mid- and long-term results for these methods [15]. The scientific information regarding VTSY is rather limited. Three studies (including 24, 43 and 10 patients, respectively) have shown a decrease in the frequency of chest-pain attacks and an increase in exercise tolerance [16–18]. Studies focusing on pathophysiological aspects of sympathetic heart denervation led to renewed interest in this method. There is a rich sympathetic network in the walls of coronaries. In standard circumstances, the muscular layers of these walls lead to dilatation under the sympathetic influence. However, vasoconstriction prevails in the atherosclerotic artery. Reflex contraction associated with the loss of endothelial integrity and transmitter changes at the terminal sympathetic endings are probably the cause of vasoconstriction. Serotonin is linked with the late effect. Serotonin is released in foci of aggregation, i.e. the site of turbulent flow. This vasoconstriction effect is successfully reduced by sympathetic blockage. An anti-ischemic effect of thoracic sympathetic blockage was clearly recorded in several experimental studies, and antiarrhythmic and positive influences on ischemic myocardium were demonstrated in several other studies. Decreased myocardial oxygen consumption, dilatation of the atherosclerotic artery, and spread of the myocardial capillary bed were the most important outcomes of these studies that were used lately in clinical practice. It is a well established fact that a long-term increase of sympathetic nervous activity (SNA) correlates with coronary, cardiovascular and general mortality of a population [19]. Patients with unstable angina have higher levels of norepinephrine. Left ventricular dysfunction is associated with the highest increase of catecholamines during ischemia [20]. Lowered life expectancy of patients with left ventricular dysfunction or chronic heart failure is strongly correlated with levels of circulating catecholamines. Heart rate (SNA activity marker) and its variability in patients who suffered myocardial infarction are strong predictors of death [21]. Catecholamines increase the risk of malignant arrhythmias and sudden death by reducing the ventricular fibrillation threshold. A positive effect resulting from decreased SNA activity can be expected on the basis of these facts, and represents an outcome that is reached neither by pharmacological or alternative venues.

Table 1
Demographic and preoperative clinical data

Number of patients	10
Age (Y, mean±S.D. and range)	60.8±10; (47–81)
Patients of male gender	10 (100%)
Ejection fraction (%, mean±S.D. and range)	42±9.9; (27–58)
Lung vital capacity (L, mean±S.D. and range)	3.2±0.37; (2.6–3.8)
Arterial hypertension	6 (60%)
Diabetes mellitus	3 (30%)
Hyperlipidemia	10 (10%)
Smoking in history	9 (90%)
AMI in history	9 (90%)
PTCA	7 (70%)
CABG	6 (60%)
PTCA and CABG	6 (60%)
Pacemaker	1 (10%)
ICD implantation	2 (20%)

2. Methods

2.1. Patients

Ten male patients underwent VTSY treatment in 1998–2002, and represented an average age 60.8 years (47–81 years). All patients presented severe angina, in spite of maximal pharmacological therapy, and were unsuitable for either PTCA or CABG. Six patients had a history of CABG, one underwent PTCA repeatedly, and three were not suitable for any intervention on their coronaries following diagnosis. There was a reduction in the global ejection fraction in all patients, with the level being below 30% in two patients (yet not fulfilling the heart transplant indication criteria). The characteristics of patients are shown in Table 1. Their pain was estimated at the level 10 on the visual analog scale (VAS). There was one patient with a permanent pacemaker, and two with an ICD implant because of sustained ventricular tachycardia in the group. Preoperative evaluation included aspects of personal history, a physical examination, antero-posterior and lateral chest X-rays, and the use of a 12-lead ECG, spirometry, echocardiography, 24-h Holter monitoring, ergometry, and the evaluation of catecholamine levels in the last five patients. Resting heart rate was 86 bpm, and average amount of ventricular premature beats (VPB) during the Holter 24-h monitoring period was 29/h. Intensity is the main characteristic of the pain experienced by our patients; a VAS was used for its evaluation as it is the predominant method. Percutaneous sympathetic thoracic blockage was performed on the day of admission as a test for VTSY effects, and the procedure was cancelled if bradycardia was detected during telemetry. The inclusion and exclusion criteria for VTSY are shown in Tables 2 and 3. An informed consent was obtained from all the patients and the institutional ethics committee approved this type of treatment.

Table 2
Inclusion criteria for VTSY

Coronary artery angiography within last 3 months
Chronic coronary artery disease
Angina pectoris CCS III-IV
Optimal medical treatment (antiplatelets, Beta-blockers, Ca-antagonists, ACE-inhibitors or
AT1-antagonists, long-acting nitrates)
Patient not suitable for PCI or CABG after discussion with cardiologists and cardiac surgeons

Table 3
Exclusion criteria for VTSY

Myocardial infarction or unstable AP in the last 3 months
Relevant valvular heart disease
Symptomatic heart failure NYHA II
Significant pleural adhesions
Other reason for chest pain (e.g. vertebrogenic algic syndrome)

2.2. Technique

The procedure was carried out under general or combined anesthesia with selective single-lung ventilation, and consequently, all the functional tests must meet the criteria for this type of ventilation. Insertion of the thoracic port through the skin and intercostal space produces a pneumothorax that allows videothoracoscopy. The elasticity and absence of adhesions of the lung allow its full collapse. When adhesions between parietal and visceral pleura occur, in addition to the presence of low pulmonary elasticity, a required pneumothorax of 6–10 cm cannot be achieved. An endoscopic approach cannot be used in the presence of flat apical adhesions. Striated adhesions can be sharply dissected using another 5 mm port for instruments. Three to four ports were inserted for VTSY and a rigid 30° endoscope (Olympus A 5195A/OTV-S6; Olympus Optical Co, Ltd, Tokyo, Japan) was used for visualization. The usual site for optical port was the 3rd intercostal space lateral to pectoralis major muscle and instrumental ports were in 5th intercostal spaces in posterior axillary line and 3–4 cm anterior to anterior axillary line. However, the precise localization and number of instrumental ports was obtained only after target site inspection with camera. The capnopleural overpressure was at most 6–8 mmHg with a switch-off feed-back at 10 mmHg. Overpressure in the pleural cavity is produced by carbon dioxide in a manner similar to a laparoscopy involving reduced lung elasticity (interstitial pathology), and so the collapse of the lung can be augmented. The use of capno-pleural overpressure immediately influences hemodynamics, and can only be carried out safely with continual monitoring and prompt correction by an experienced anesthesiologist (in our opinion, a cardio-anesthesiologist). A pneumothorax is produced at the operated hemithorax and only the contra-lateral lung is being ventilated, with its function being limited by the weight of the mediastinum because of the patient's positioning. Bilateral gangliectomy at the levels Th2-Th4 was performed in eight patients. Transection of interganglia fibers was performed in two patients because of unfavorable anatomical conditions. Electrocautery was used in the first five patients, and a harmonic scalpel was used in all of the following procedures. Both pleural cavities were drained in all patients.

2.3. Statistical analysis

The results were analyzed using the paired *t*-test to compare the baseline and six-month follow-up data. Statistical significance was estimated at the $P<0.05$ level. Results were expressed as the median $\pm$ S.D. (standard deviation).

3. Results

An average hospital stay was 4.1 days (range 3–6), with no deaths occurring in our group. The intercostal artery was injured in one patient, and treated by hemoclip. Capnopleural overpressure had to be discontinued because of hypotension, tachycardia or a decrease in oxygen saturation in three patients. Following paresis of the right diaphragm in one patient operated with electrocautery, we preferred the use of the harmonic scalpel. An apical pneumothorax resulted on one occasion following accidental disconnection of the chest drainage system. Six-month results are summarized in Table 4. Pain decreased on average from level 10 to 4.1 according to the VAS ($P<0.05$). The preoperative angina class dropped from an average of 4 to a postoperative average of 2.4 ($P<0.05$). The frequency of angina attacks was significantly reduced (chest-pain attacks per week has decreased from 43.4 to 17.6,

Table 4
Clinical status of patients before and after VTSY

Patient no.	Angina score before VTSY	Angina score after VTSY	AP (CCS) before VTSY	AP (CCS) after VTSY	Angina/week before VTSY	Angina/week after VTSY
1	10	5	4	2	30	18
2	10	10	4	4	100	100
3	10	4	4	2	28	10
4	10	5	4	3	35	14
5	10	3	4	2	56	7
6	10	2	4	2	28	5
7	10	4	4	3	43	14
8	10	3	4	2	50	7
9	10	2	4	2	36	0.5
10	10	3	4	2	28	1
Average	**10**	**4.1**	**4**	**2.4**	**43.4**	**17.6**

Angina score – angina intensity estimated using a Visual Analog Scale; Angina/week – number of chest-pain attacks during one week

Table 5
Patients' medication before and six-month after surgery

ASA (acetylsalicylic acid)	10 (100%)	10 (100%)
Beta-blocker	10 (90%)	10 (90%)
Ca-antagonist	9 (90%)	9 (90%)
Long-acting nitrate	10 (100%)	10 (100%)
ACE-inhibitor	6 (60%)	5 (50%)

$P<0.05$), as well as the consumption of nitroglycerin tablets. Chronic oral medication given before and six months after VTSY is summarized in Table 5. The exercise tolerance was measured by a walk-test prior and six months after VTSY. The walking distance has increased from 110 ± 23 m to 220 ± 26 m ($P<0.05$). The extent of sympathectomy was strongly correlated with the regression of angina. When only a transection of interganglia connection fibers was performed (in two patients, No. 1 and 4), its effect was inadequate. A decrease in pain did not occur in one patient with severe chronic back pain who addictively used a combination of pain-killers. Reflex truncal hyperhidrosis, considered a possible side-effect of thoracic sympathectomy, was referred by one of our patients. A statistically significant drop in the level of norepinephrine occurred in all assessed patients (3.3 vs. 1.2 pmol/ml, $P<0.05$; Fig. 1), as well as an observed decrease in the average number of VPB during Holter monitoring (11/h, $P<0.05$) and a drop in the resting heart rate (67 bpm, $P<0.05$). LV ejection fraction, spirometry and plasmatic levels of dopamine and epinephrine did not show any changes.

4. Discussion

We strongly believe that even in the current era of modern therapeutic methods (i.e. stem-cell therapy, mechanical assist device, etc.), patients with refractory angina should not be beyond our interest. In particular, cardiologists who frequently face patients with refractory angina are limited in their decision making when all standard methods have been exhausted, and resort to prescribing pain-killers with increased dose. Personal experience or published data stand at the base of their decision, and they are required to choose from modern alternative therapeutic methods. In our opinion, VTSY is a favorable alternative method. In the hands of an experienced and skilled team involving a thoracic surgeon and anesthesiologist, VTSY presents a one-stage procedure with a short ICU and overall hospital stay, with an early discharge for the patient. From the point of view of the extent of this procedure, we advocate bilateral sympathectomy at the levels Th2-Th4. Interruption of interganglia fibers at the levels of proximal ganglia and interruption of the communicant branches of Th2-Th4 ganglia is one of the possibilities. During the VTSY, Th2 is the first ganglion we can identify. Due to the location of the Th1 ganglion in the extra-pleural space, it cannot be reached without opening of the parietal pleura during thoracoscopy. In our first four patients we performed chemical destruction of the stellate ganglion simultaneously, but thoracoscopy revealed that the needle did not reach the ganglion, and for the most part, only soft tissue had been infiltrated. In two cases involving the interruption of interganglia fibers, only a 50% reduction of angina occurred. Therefore, our target at present is to achieve complete bilateral sympathectomy. In cases of an insufficient decrease in angina following VTSY, we suggest CT-guided radiofrequency ablation or mediastinoscopic alcoholic blockage of the retrocardial plexus. We were not forced to use these methods since VTSY was a very pleasant surprise for the majority of our patients, and furthermore, proved the ideas on which our research was based. To verify the effect of sympathectomy, we introduced in 2003 a method of myocardial scintigraphy using metaiodine-benzyl-guanid (I-123 MIBG) in cooperation with the Radioisotope Department of IKEM (Institute for Clinical & Experimental medicine, Prague, CR). Not being a new method in CAD treatment according to recent pathophysiological findings, thoracic sympathectomy and the development of mini-invasive endoscopic techniques is undergoing a renaissance. There are still many unanswered questions. Is increased oxygen supply related to augmented coronary flow? Is there a reduction in the number of alpha1 receptors responsible for coronary vasoconstriction? Do we improve repolarization and depolarization scatter? Transmission of the information at the level of sympathetic neural endings is life-important, and consequently, it is a process that is secured by several alternative systems. Activity of co-transporters (neuropeptide Y, ATP) increases in case of pharmacological blockage of norepinephrine release to prevent attenuation of information transmission. Neuropeptide Y is responsible for vasoconstriction; ATP is responsible for dysrhythmias and neuro-cardiogenic syncope [22]. The question remains whether it is too late for the pharmacological blockage of receptors during refractory angina. This problem can be solved by VTSY. While thinking about an improvement in the prognosis of patients, parasympathetic stimulation that leads to a drop in heart rate had to be considered. Thus, the prospect of vagal stimulation had arisen (estimated price of the stimulator is US$20,000). It has been proved that cholinergic stimulation works well on an animal model, but not on one involving humans. This method is used with good results in pharmacoresistent epilepsy. According to its positive effect, we can consider the broader implications for VTSY. We can think about simultaneous myocardial

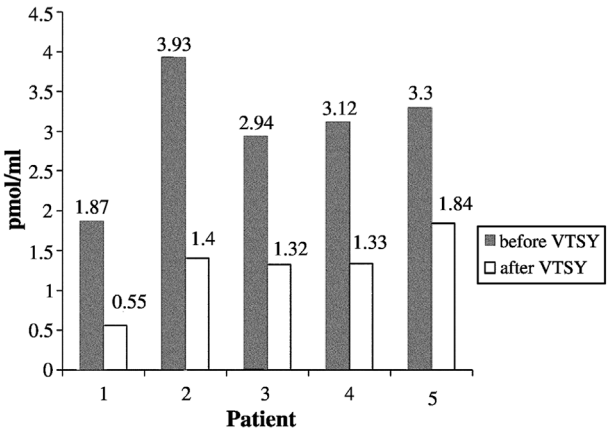

Fig. 1. Level of plasmatic norepinephrine before and six months after VTSY. Before VTSY 3.03 ± 0.5 pmol/ml. After VTSY 1.28 ± 0.3 pmol/ml ($P<0.05$).

revascularization and thoracic sympathectomy in patients scheduled for cardiac surgery. Vasospasms decrease bypass flow and thus increase the probability of thrombi formation. Reduction in the occurrence of vasospasms can prevent graft occlusion. Blockage of alpha-1 receptors can be used in the treatment of vasospastic angina. We can discuss the possible combination of VTSY and ICD implantation, which according to improved electrical myocardial stability; can enhance the longevity of ICD [23]. The duration of sympathectomy effects is a question for further experimental and clinical trials.

5. Conclusion

Based on the clinical evidence of a small cohort of ten patients with refractory angina, VTSY improved the quality of their life by lowering the frequency and intensity of angina. We think that in era of an increasing number of patients with severe angina unsuitable for conventional therapy, VTSY is a promising method for refractory angina treatment. This method can be performed with a short hospital stay, low morbidity, and in our small group of patients, with zero mortality, and dissolves the complaints of patients concerning a limited quality of life. Finally, we must point out the very high risk associated with any available therapeutic method for patients with refractory angina. We believe that the improved quality of life among our patients advocates the use of VTSY treatment. A follow-up of a larger group of patients after VTSY treatment is needed to determine whether this method is only palliative, or if it can even improve the prognosis of patients with refractory angina. Five years follow-up of our small group will be assessed soon.

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