CHAPTER 8

Treatment of resistant Raynaud’s phenomenon with single-port thoracoscopic sympathectomy: a novel minimally invasive endoscopic technique

Anniek M. van Roon
Michiel Kuijpers
Saskia C. van de Zande
Amaal Eman Abdulle
Arie M. van Roon
Reinhard Bos
Wobbe Bouma
Theo J. Klinkenberg
Hendrika Bootsma
Mike J.L. De Jongste
Massimo A. Mariani
Andries J. Smit
Douwe J. Mulder

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ABSTRACT

Objectives: To assess the minimally invasive single-port thoracoscopic sympathectomy (SPTS) feasibility and efficacy in patients with treatment-resistant RP.

Methods: SPTS was performed unilaterally on the left side in 8 patients with RP (6 males, 2 females, with a median age of 45.2 years). Five patients had primary and three had secondary RP. Perfusion effects in the hands were assessed at baseline and after 1 month by using a cooling and recovery procedure, and by using laser speckle contrast analysis (LASCA). Number and duration of RP attacks were reported over a two-week period.

Results: Patient-satisfaction was 100% after surgery. After surgery, a unilateral improvement in perfusion was observed in the left hand compared to the right hand, with cooling and recovery (p=0.008) and with LASCA (p=0.023). In addition, the number and duration of the attacks in the left hand decreased compared to the right hand (both p=0.028). No serious adverse events occurred in a follow up period of at least ten months.

Conclusion: SPTS is feasible and can be effective in improving hand perfusion in patients with Raynaud’s. However, long-term efficacy needs to be established.
INTRODUCTION

Raynaud’s phenomenon (RP) is a vasospastic disorder, characterized by discoloration of the extremities provoked by cold or emotional stress.\textsuperscript{1} RP may have a tremendous impact on quality of life.\textsuperscript{2} However, treatment options for RP are limited. Conventional medical treatment mainly consists of vasodilatory drugs, which are not effective in all patients and may induce undesired side-effects.

In selected cases, a surgical intervention by means of sympathectomy can be considered. During this procedure, the sympathetic nerve traversing the thoracic cavity is dissected, which lowers sympathetic tonus and subsequently induces vasodilatation. Different approaches and techniques for this procedure have been studied and applied over the years, and although the surgical technique has improved overtime, considerable surgical risks remain.\textsuperscript{3-5} In our centre, a novel single-port thoracoscopic sympathicotomy (SPTS) has been developed in order to minimize surgical impact.\textsuperscript{6} SPTS, initially developed for patients with hyperhidrosis, significantly limits surgical burden and further minimalizes risks when compared to conventional multiple-port sympathectomy. Furthermore, SPTS implicates transection of the nerve, instead of a surgical removal of a part of the nerve itself. Therefore, SPTS might be a promising novel treatment option in patients with treatment-resistant RP.

In this study, we sought to assess the feasibility of SPTS in patients with RP resistant to all other conventional therapies. In addition, we analysed the effects of the SPTS on hand perfusion, with a cooling and recovery procedure and laser speckle contrast analysis (LASCA), and with questionnaires. Patients served as their own controls, as they received a unilateral left-sided SPTS.

PATIENTS AND METHODS

Patients

Patients were recruited at, or especially for this study referred to, the outpatient clinic of the vascular medicine department of the UMCG. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The study was approved by
the local ethics committee (Groningen, The Netherlands, approval number 2015.044), and all patients gave written informed consent. The study was registered at http://www.clinicaltrials.gov (NCT02680509). RP patients were eligible when they were 18 to 65 years of age, and had unsatisfactory effects of prostacyclin-analogue infusion, or relative contra-indications for prostacyclin treatment. Patients were excluded when they were at a higher risk of complication following unilateral lung-deflation and re-insufflation (e.g. underlying pulmonary disease or a history of smoking of over 20 pack years), signs/symptoms of peripheral artery disease, severe concomitant diseases, previous intra-thoracic pleural drainage, previous thoracic surgery, pregnancy, or unsuitable anatomy due to severe physical malformations. Patients were classified as primary RP when nailfold capillaries were normal and serology was negative. Systemic sclerosis (SSc) was classified according to the ACR/EULAR criteria, and mixed connective tissue disease (MCTD) according to the criteria proposed by Kasuwaka et al.\textsuperscript{7,8}

**Surgical procedure**

We chose to perform the procedure in every patient left-sided, and so makes the procedure independent of most affected side. For the SPTS we adopted a semi-Fowler’s position, as published previously, reducing duration of surgery and improving patient safety.\textsuperscript{6} Patients were seated at a 45° angle above the horizontal plane, to help folding the collapsed lung in a dorso-caudal direction, which creates a complete view of the surgical field.

General anaesthesia was administered and patients were intubated with a single lumen endotracheal tube. The procedure was performed during apnoea. Following local infiltration with bupivacaine, a 7 mm incision was made in the left anterior axillary line. After deflation of the lung, a 5 mm trocar was inserted through the third intercostal space, just posterior to the major pectoral muscle. A 5 mm scope (Karl Storz, Tuttingen, Germany)\textsuperscript{5} and cautery hook were then introduced. The first and second rib were identified, as well as the sympathetic chain running along the ‘neck’ of the ribs. The part of the sympathetic chain overlying the rib was transected with diathermy at high costal level, sparing the sympathetic ganglia and thus performing an R3-sympathicotomy. (Figure 1A-C)
Figure 1. **Single-port thoracoscopic sympathicotomy of the third rib**

**A/B:** Intra-operative view of the sympathetic chain running down the dorsal thoracic wall, lateral of the costo-vertebral junction. In the left upper corner the subclavian artery can be seen. **C:** Detail of the 3rd rib after R3 sympathicotomy. **D:** Left and right difference of the hands of a patient during a Raynaud’s attack, one month after left-sided R3 sympathicotomy.

The transection was extended 2 cm laterally over the rib to transect any accessory nerve fibres. The surgical procedure was completed by insertion of an 8 mm French thoracic drain through the same access port, re-insufflation and recruitment of the collapsed lung under direct vision and removal of the drain under positive end expiratory pressure.
A thoroughly placed subcutaneous string suture ensured airtight incision sealing. The skin was sutured intracutaneously.

**Vascular measurements**

All vascular measurements were performed one or two days prior to the surgery (baseline) and one month after, in a temperature controlled room by one vascular technician.

The cooling and recovery procedure was performed on both hands, as described previously. In short, photo-electric plethysmography (PPG) sensors were placed on all fingertips to assess blood flow. Both hands were submerged in water up till the radio carpal joint. Every 4 minutes, the water was cooled by 3°C, from 33°C to 6°C, or until the patient could not tolerate the pain anymore. After cooling, the blood flow was assessed every minute during a 10-minutes recovery period.

LASCA was performed to measure peripheral blood perfusion, at room temperature (23°C), on both hands using a PeriCam PSI System (PeriMed, Jarfalla, Sweden). Data acquisition and analysis was performed making use of PIMSoft (PeriMed, Jarfalla, Sweden). Perfusion was processed as numerical values in perfusion units and color-coded-images. A total of one minute was recorded per hand, of which a stable period of 10 seconds was assessed. Two regions of interest were selected, ROI1 entailed the index, middle and ring finger distal from the distal interphalangeal (DIP) joint; and ROI2 the dorsum of the hand. The perfusion gradient was calculated by subtracting ROI2 from ROI1, as described previously.

**Patient reported outcomes**

The number and the duration of RP attacks were assessed for each hand separately in a Raynaud diary over a period of 14 days, in the two weeks immediately prior to the surgery and two weeks prior to the visit one month post-operatively.

**Statistical methods**

Statistical analysis was performed using The Statistical Product and Service Solutions (SPSS; version 23, Released 2013, IBM Corp., Armonk, NY, USA). Differences in questionnaire scores before and after surgery were compared with a Wilcoxon signed-
rank test. Differences in vascular measurements, and RP attack frequency and duration, between baseline and one month post-operatively of each separate hand were calculated and are referred to as delta. Differences between the deltas of left and right were tested with Wilcoxon signed rank test. Data is shown as median (IQR) or number (%). P-values <0.05 were considered statistically significant.

RESULTS

Patients
Eight patients were included in the study, 6 males/2 females, with a median (IQR) age of 45.2 (30.2–55.3) years, body mass index of 23.9 (23.4–26.8) kg/m², and RP duration of 7.0 (2.5–14.3) years. Five patients suffered from primary RP, and three patients had RP secondary to connective tissue disease [MCTD (n=2) and, limited cutaneous SSc (n=1)]. Of these patients, all had unsatisfactory effects of calcium channel blockers, three experienced side effects as well. Seven patients had unsatisfactory effects and/or severe side effects of iloprost or prostacyclin infusions. One patient reported an unsatisfactory effect of alpha-blockers. All patients their right hand was dominant. Only the patient with SSc had a history of digital ulceration, with an (almost healed) ulcer at baseline visit, which was healed one month post-operatively. None of the patients had (a history of) critical ischemia. Patients complaints were symmetrical, which was confirmed by comparable left and right baseline values of the vascular measurements and duration and number of attacks (table 1).

Surgery, safety and adverse events
The mean intubation time was approximately 21 minutes, during which the mean time of the procedure itself was about 8 minutes. No complications occurred during surgery. After surgery no serious adverse events occurred. The day following the procedure, all patients were discharged from hospital. After discharge, one patient experienced a subjective swelling of the left hand (hyperaemia), which resolved spontaneously within one week. One patient reported a dry skin patch at the fingertips of the left hand three months after surgery (during the winter season), which also resolved spontaneously, within five months. Two patients reported a mild increase in sweating, the months following surgery [dorsal side of the trunk region (n=2), chest (n=1), and axillary (n=1)].
Vascular measurements
Figure 2 shows the mean number of fingers of one hand, with perfusion during the cooling and recovery procedure. The mean ischemic time of five fingers decreased in the left hand compared to the right hand (table 1). The mean temperature at which five fingers lost perfusion decreased in the left hand compared to the right hand (table 1). LASCA showed that the perfusion gradient increased in the left hand compared to the right hand (table 1).

Patient reported outcomes
Patient satisfaction was 100% after surgery. Figure 1D shows how remarkable the results of surgery can be one month after SPTS of the left hand. The total number and duration of attacks of the left hand over a period of 14 days was reduced compared to the right hand (table 1). Six patients did not experience any attacks in the left hand after surgery, and in the two patients who did, both frequency and duration of attacks were reduced compared to attacks in the right hand.

Figure 2. Cooling and recovery procedure
Mean number of fingers per hand with normal perfusion during the cooling and recovery procedure pre-operatively (baseline) and one month post-operatively after left-sided SPTS.
Table 1. Vascular and patient reported outcomes for left (intervention) and right (control) hand at baseline and one month post-operatively

|                        | LEFT                      | RIGHT                      |
|------------------------|---------------------------|----------------------------|
|                        | Baseline                  | One month post-operatively | Delta                      | Baseline                  | One month post-operatively | Delta                      |
| Vascular measurements  |                           |                            |                            |                           |                            |                            |
| Mean ischemic time in minutes | 23.9 (15.3–28.7)        | 10.8 (5.0–17.5)             | -10.4* (19.8– -4.7)       | 22.0 (12.7–30.3)        | 21.8 (15.4–33.7)             | -0.1* (-4.0–9.4)            |
| Mean temperature of loss of perfusion in °C | 19.6 (17.4–22.5)        | 16.2 (12.0–17.0)             | -7.7* (-9– -1.8)         | 18.8 (17.7–24.3)        | 21.3 (17.6–26.7)             | 0.7* (-1.9–6.5)             |
| Perfusion gradient in perfusion units | 21.1 (-4.4–35.7)        | 29.3 (20.4–42.5)             | 14.0* (0.9–23.7)        | 25.6 (-8.5–47.9)        | 4.4 (-2.6–24.5)              | -15.5* (-30.9–11.9)         |
| Patient reported outcomes |                           |                            |                            |                           |                            |                            |
| Total number of attacks | 13.0 (5.0–23.0)          | 0.0 (0.0–0.0)                | -11.0* (-23– -5)         | 14.0 (10–24)            | 10.0 (8.0–25.0)              | -3.0* (-7.0–6.0)            |
| Total duration of attacks in hours | 3.0 (1.5–18)           | 0.0 (0.0–0.1)                | -3.0* (-18– -1.4)        | 2.9 (1.3–6.7)           | 2.0 (1.0–6.6)                | -0.9* (-5– -0.1)            |

Data are in median (IQR)

**Delta:** difference between baseline and one month post-operatively (one month – baseline)

*p*<0.05 between delta of left and right hand
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DISCUSSION

In this study we have shown that the described novel SPTS procedure is feasible and effective in improving hand perfusion in patients with treatment-resistant Raynaud’s phenomenon, although the outcomes are first observations at an early stage, and longer follow-up in larger patient cohorts is needed. The most striking result of the present study was the significant improvement of left hand perfusion in all patients, during a cooling and recovery procedure, one month after SPTS. In addition, perfusion of the left fingertips at room temperature also increased, as assessed with LASCA. Finally, patients were very satisfied with the result and reported less and shorter RP attacks of the left hand.

Current treatment options (i.e. intravenous prostacycline) are expensive, very time-consuming, and can be a great burden for patients. Therefore, SPTS, with very limited side-effects, is an attractive and promising treatment option. With regards to conventional surgical intervention, Coveliers et al. (2011) found that 89% of the primary and secondary RP patients had beneficial short-term effects following conventional sympathectomy. Moreover, 59% of the primary RP patients and 89% of the secondary RP patients reported beneficial long-term effects (>18 months). Given the minimal invasive character of our SPTS, and comparable short-term results to those reported by Coveliers et al. (2011), our method may offer to be a favourable and safe therapeutic alternative to sympathectomy.

The main limitation of this study is the short follow-up and relatively small sample size. Despite this limitation, we were able to demonstrate clear differences between the intervention side and control side. As there is no standardized validated method to assess perfusion in RP, we used the cooling and recovery procedure and LASCA, which were performed by the same technician using the same protocol before and after surgery. This ensured that changes overtime would not be influenced by inter-observer and technical differences. Perfusion measurements, especially of extremities, are always limited by environmental influences such as the weather and room-temperature (although performed in a temperature controlled room). However, because we compared left with right, the influence of this was kept to a minimal.
In the current study no patients with advanced connective tissue diseases participated. However, patients with advanced disease may experience severe RP symptoms with even critical digital ischemia. The results of Coveliers et al. (2011) suggest that these patients can benefit most from this procedure, as sympathectomy maximizes tissue preservation. Furthermore, the characteristics (i.e., age, disease duration and gender) of the primary RP patients were not typical for the disease. This is due to the fact that we included patients with severe complaints, and this might influence the generalizability of our results to the typical patient with primary RP. However, at this stage the SPTS is not recommended for typical primary RP patients, and the procedure is for now an option for patients with such a nature of complaints that it limits daily activities and are resistant to conventional treatment. Therefore, future studies should also include patients with more extensive connective tissue diseases as well as less severe primary RP.

In conclusion, one month after unilateral SPTS, the number of RP attacks was reduced and perfusion of the treated hand increased. Given the reported beneficial effects as well as the limited adverse events, SPTS appears to be a promising treatment option for patients who do not respond well to conventional vasodilatory drug treatment. Follow-up studies are on-going to investigate the long-term effects of SPTS and to optimize treatment strategies for different subgroups of RP patients.
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SPTS as treatment for Raynaud
