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Treatment of resistant Raynaud's phenomenon with single-port thoracoscopic sympathicotomy: One-year follow-up

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ABSTRACT

Objective: Follow-up of patients with treatment-resistant Raynaud's phenomenon (RP) one-year after single-port thoracoscopic sympathicotomy (SPTS).
Methods: Eight patients (six males, two females, median age of 45 years) with treatment-resistant RP underwent left-sided SPTS at the third rib (R3), unilaterally. Questionnaires were taken, and number and duration of RP attacks were reported over a 2-week period. Perfusion was assessed with a cooling and recovery procedure at baseline and one year after SPTS. Furthermore, laser speckle contrast analysis, pulse wave velocity, heart rate variability and nailfold capillary microscopy were performed.
Results: One year after SPTS the duration of the attacks of was reduced with 1.9 h in the left hand versus 0.3 h in the right hand. Furthermore, three aspects of the questionnaire showed a significant improvement (role limitations due to physical health ($p = 0.017$), pain ($p = 0.027$) and physical functioning ($p = 0.025$)). The total area under the curve of the total cooling and recovery procedure of the left hand was larger one year after surgery (101 (75–140) at baseline versus 118 (95–190) one year post-operatively, $p = 0.012$), implying a better perfusion in the fingers. This was mainly due to the improvement during the recovery phase (21 (1–41) at baseline versus 38 (24–43) one year post-operatively, $p = 0.028$).
Conclusion: One year after unilateral R3 SPTS the benefit with regard to the majority of outcome variables persisted, though some effects seem to attenuate. Long-term effects and long-term follow-up results will be investigated in an on-going study.
Clinical trial registration number: NCT02680509.

Introduction

Raynaud's phenomenon (RP) usually results in discoloration of the extremities when provoked by cold or emotional stress [1]. The most common form of RP is primary (idiopathic), which is benign. Secondary RP occurs when an underlying disease can be identified. There are multiple causes, of which connective tissue disease (CTD) are the most common. Patients with RP secondary to CTD tend to have damage of the (micro)vasculature, which can be assessed by using nailfold capillary microscopy. Some patients do not respond to conventional therapies, such as lifestyle interventions and vasodilatory medication. These patients are confronted with limited options for treatment. However, for patients with RP resistant to first line treatment, thoracic sympathectomy is reported to be an effective treatment [2–4]. Although surgical techniques have improved over the years, this procedure has become less popular due to the risk of complications and concern for attenuation of long-term effectiveness [3–5]. In a previous study we have shown that minimally invasive Single-Port Thoracoscopic Sympathicotomy (SPTS) objectively and subjectively improves treatment-resistant RP, after one month [6]. This procedure for treatment-resistant RP is minimally

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invasive and potentially highly effective, because it specifically targets the sympathetic nerve at the third rib (R3), while leaving the ganglia untouched [7]. The procedure was only performed on the left side in the pilot study, which objectively resulted in improvement of left-hand perfusion in all patients after one month, when compared to the right hand. Furthermore, patient satisfaction after surgery was high and RP attacks of the left hand were less frequent and of shorter duration. Previous studies have shown that long-term effects of conventional sympathectomy is stable in the long run in the majority of patients [2,4]. We have previously published the one-month results of SPTS for treatment-resistant RP in a concise report [6]. In the current study we sought to report the one-year follow-up results of SPTS for treatment-resistant RP in the same cohort of patients. In addition to patient-reported outcomes and objective measures of (cold-induced) hand perfusions loss, we aimed to investigate off-target systemic sympathetic effects by measuring systemic vascular resistance and cardiac sympathetic activity.

Methods

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, 2013 and was approved by the local hospital ethics committee UMCG (Groningen, The Netherlands, approval number 2015.044). All patients provided written informed consent. The study was registered at http://www/clinicaltrials.gov/ (NCT02680509).

Patients with treatment-resistant RP were included. Patients underwent vascular measurements one or two days prior to surgery and one month and one year after surgery. Vascular measurements consisted of a cooling and recovery procedure, Laser Speckle Contrast Analysis (LASCA), Nailfold Capillary Microscopy (NCM), and Pulse Wave Velocity (PWV). For a more detailed description of the in- and exclusion criteria, the surgical procedure, LASCA and patient-reported outcomes we refer to our previously published concise report on immediate outcome after SPTS for treatment-resistant RP [6]. In addition, treatment-resistant RP was defined as an unsatisfactory response on, or a contra-indication to medication or experiencing major side effects that lead to termination of medication use. For the cooling and the recovery procedure we refer to van Roon et al. [8].

Surgical procedure

In brief, eight patients underwent a unilateral left-sided single-port R3 sympathicotomy using cautery on the third rib level (R3). Patients were positioned in a semi-Fowler's position. The procedure was performed under general anesthesia and patients were ventilated using a single-lumen endotracheal tube. The procedure was performed during apnea and a brief tube disconnection, which facilitates lung deflation and visualization of, and access to the sympathetic nerve. A chest drain was not required after re-insufflation. Recruitment of the collapsed lung under direct vision enables thoracic drainage under positive end-expiratory pressure and placement of an airtight subcutaneous suture. The surgical procedure performed in this study consists of a single-port access R3 sympathicotomy, an operation that can safely be performed in high-volume thoracic centres. In our hospital, mean operation room time for this procedure is around 35 min. We published the surgical technique in detail earlier [9].

Patient-reported outcomes

A Raynaud's diary was provided to the patients to score the number and duration of Raynaud's attacks for each hand separately, over a period of 14 days [10]. Patients were instructed to maintain the diary two weeks prior to surgery and two weeks prior to their one-month and one-year follow-up visit. The diary also withholds a Raynaud Condition Score, with a 0–10 ordinal Likert scale to rate the level of difficulty experienced due to RP each day.

Furthermore, patients filled out two self-reported questionnaires. First, the Health Survey Short Form 36 (SF-36) to assess the health-related quality of life [11]. This questionnaire consists of 36 items in 8 different domains (emotional well-being, energy/fatigue, general health, role limitations due to emotional problems, role limitations due to physical health, pain, physical functioning, social functioning) on a nominal and ordinal scale. Scores were recoded and item scores were added to a 100-point scale. A higher score indicates a better health status.

Second, the Health Assessment Questionnaire (HAQ) was used to assess limitations during daily life activities [12]. This questionnaire has 20 items in 8 different domains (dressing/grooming, arising, eating, walking, hygiene, reach, grip and activity) with 4 answer options (A=without any problems and D=impossible). The total score was calculated by adding up the highest score for each of the 8 items. Then the outcome was divided by 8 to calculate the total score (ranging between 0 and 3).

Cooling and recovery procedure

In brief, photoelectric plethysmography sensors were placed on all fingertips to assess blood flow. Both hands were submerged in warm water (>33 °C), up till the radio-carpal joint. First, a baseline measurement was performed when all fingers showed a good and steady blood flow. Subsequently, the water was cooled by steps of 3 °C every 4 min, beginning at 33 °C and continuing to 6 °C, or until the patient could no longer tolerate the temperature of the water. After cooling, a 10 min recovery period followed, during which blood flow was measured in all fingers, every minute. The number of fingers with normal perfusion for each time point was calculated and used as outcome measure. In addition, ischaemic time (in minutes) was calculated as the time between loss and recovery of perfusion of one finger. The average ischaemic time of all five fingers was calculated and reported as mean ischaemic time. The area under the curve (AUC) was calculated for the mean number of fingers per hand with perfusion. AUC was calculated by using the trapezoid approximation of the area during the period of cooling and during the period of recovery separately. Maximum AUC was 180 for the cooling period and 45 for the recovery period.

The ECG-signal was recorded simultaneously to assess heart rate variability (HRV), during cooling and recovery procedure. ECG signal (sampling frequency 200 Hz, approximately lead II to obtain a distinct R-peak) was recorded simultaneously to assess heart rate variability, during the cooling and recovery procedure. The last two minutes of each temperature period and recovery were used for analysis. PreCar 3.8 software [13] was used for R-peak detection and artefact correction. Time domain parameters [14] inter-beat interval (IBI, ms), standard deviation of inter-beat interval (SDNN, ms) and the root mean square of the successive differences of inter-beat interval (rMSSD, ms) were calculated using CARSPAN software [15]. Log transformed values of SDNN and rMSSD were used for analysis.

Laser speckle contrast analysis (LASCA)

In brief, LASCA was used to assess peripheral blood flow in two different regions of interest (ROI) of the hand. ROI-1 for index, middle and ring finger distal from the distal interphalangeal joint. ROI-2 for the dorsum of the hand. The perfusion gradient was calculated by subtracting ROI-2 from ROI-1.

Nailfold capillary microscopy (NCM)

NCM was performed using an Olympus BXFM set-up (Olympus, Tokyo, Japan), with Olympus CellSens software (Olympus, Tokyo, Japan). After at least 15 min in a temperature-controlled room of 23–24° C, a drop of immersion oil was placed on the nailfold to increase transparency. All digits except the thumbs were assessed. All images were analysed by a vascular technician (SZ) after study completion. In a 3 mm grid the capillary density per 3 mm, giant capillaries (>50 µm), dilated capillaries (>20 and <50 µm), neovascularisation and haemorrhages were counted. Microangiopathy Evolution Score (MES), Capillaroscopic Skin Ulcer Risk Index (CSURI) and Prognostic Index for Digital Lesions (PIDL) were assessed as described previously [16–19]. For the CSURI a cut-off value of 2.96 was used [20].

Pulse wave velocity (PWV)

Aortic PWV was determined, making use of the Sphygmocor (AtCor medical, West Ryde, Australia) at carotid-femoral measurement trajectories. A more detailed protocol was described previously [21].

Statistical analysis

Statistical analysis was performed using SPSS version 23 (IBM, Armonk, NY, USA). A Wilcoxon signed-rank test was performed to compare differences in questionnaires and diary scores, at baseline and one year after surgery. For vascular measurements, AUC, and RP attack frequency and duration, the difference (delta) was calculated between baseline and follow-up. A Wilcoxon signed-rank test was performed to test differences between the delta of the left and right hand. A one-way ANOVA was used to assess differences in heart rate variability during the cooling and recovery procedure. As factor, blocks of 120 s were used, dependent variables were mean inter beat interval (IBI), lnSDNN (standard deviation of the normal-to-normal) and lnrMSSD (root mean square of successive differences). Furthermore, a one-way ANOVA with visit as factor was used to compare different visits. This was performed for each block separately; each block comprises data from one temperature (i.e. 33 °C to 15 °C and recovery). Data of 12 and 6 °C were left out because of missing data due to premature ending the cooling procedure. Bonferroni correction was used as a post-hoc test to analyze differences between visits. Data are shown as median (IQR), number (%) or mean (SD). *P*-values < 0.05 were considered statistically significant.

Results

Patients, surgery, safety, and adverse events

Data for patients and surgery, safety and adverse events have been reported in our previous paper [6]. In brief, eight patients were included in the study, six males and two females (all non-smokers), with a median (IQR) age of 45.2 (range 30.2–55.3) years, body mass index (BMI) of 23.9 (23.4–26.8) kg/m^2, RP duration of 7.0 (2.5–14.3) years and number of days between baseline visit and one-year visit was 365 (364–375) days. No new adverse events occurred after one year follow-up. All patients, except one, had at least one episode of treatment with iloprost infusions. None of the patients had a history of digital sympathectomy. No vasodilatory drugs or other additional treatments were initiated during the study. No digital ulcers occurred in any of the patients during the study period.

Patient-reported outcomes

The Raynaud's diary and questionnaires outcomes are shown in Table 1. The duration of Raynaud's attacks of the left hand over a period of 14 days was reduced when compared with the right hand, one year after surgery [left delta -1.9 (-15.3–-1.4)h versus right delta −0.3 (−1.6 to 13.7)h, $p = 0.028$]. Moreover, a reduction trend was observed in the total number of attacks of the left hand, when compared with the right hand, over a period of 14 days [left delta -3.0 (-23.0–1.0) versus right delta 1.0 (-1.0–13.0, $p = 0.058$].

The SF-36 questionnaire showed an improvement in three categories one year after surgery; role limitations due to physical health [baseline 50 (0–75) versus one year 100 (81.3–100), $p = 0.017$], pain [baseline 67.5 (38.1–75) versus one year 67.5 (60–90), $p = 0.027$] and physical functioning [baseline 81.3 (57.5–90) versus one year 90 (80–100), $p = 0.025$]. The Raynaud Condition Index (RCI) of both hands showed no significant difference between baseline [3.5 (2.1–5.9)] and one year after surgery [3.2 (1.6–4.7), $p = 0.674$]. After study completion (one year after surgery) all patients voluntarily opted to undergo R3 SPTS on the right side.

Table 1
Outcomes of the diary and questionnaires before and after left-sided R3 SPTS.

	Baseline	One month post-operatively	One year post-operatively	One month versus baseline (V2–V1)	One year versus baseline (V3–V1)
SF-36					
Emotional well-being	80 (76–84)	84 (77–94)	84 (80–91)		
Energy/fatigue	55 (42–80)	63 (56–79)	58 (51–69)		
General health	48 (36–64)	58 (46–69)*	53 (36–65)		
Role limitations due to emotional problems	100 (75–100)	100 (100–100)	100 (100–100)		
Role limitations due to physical health	50 (0–75)	63 (6–75)	100 (81–100)*		
Pain	68 (38–75)	78 (51–78)	67.5 (60–90)*		
Physical functioning	81 (58–90)	90 (80–95)	90 (80–100)*		
Social functioning	81 (53–97)	94 (75–100)	100 (78–100)		
HAQ					
	0.13 (0.00–0.69)	0.063 (0.00–0.22)	0.00 (0.00–0.31)		
Raynaud diary					
Raynaud condition score	3.5 (2.1–5.9)	2.6 (2.1–4.4)	3.2 (1.6–4.7)		
Total number of attacks *left hand*	13 (5–23)	0* (0–2)	2 (0–9)	−11.0 (−23–−5)$^+$	−3.0 (−23.0–1.0)
Total duration of attacks in hours *left hand*	3.0 (1.5–18.0)	0.0* (0.0–0.1)	0.1* (0.0–1.2)	−3.0 (−18.0–−1.4)	−1.9 (−15.3–−1.4)
Total number of attacks *right hand*	14 (10–24)	10 (8–25)	15 (13–22)	−3.0 (−7.0–6.0)	1.0 (−1.0–13.0)
Total duration of attacks in hours *right hand*	2.9 (1.3–6.7)	2.0 (1.0–6.6)	1.6 (1.1–20.3)	−0.9 (−5.0–−0.1)	−0.3 (−1.6–13.7)

*$p < 0.05$ between visit and baseline
$^+p < 0.05$ between delta of left and right hand, V = Visit, SF = Short Form, HAQ = Health Assessment Questionnaire

Vascular measurements

Figs. 1 and 2 show the results of the cooling and recovery measurements for the left and right hand, respectively. The total AUC for the left hand was larger one year after surgery ($p = 0.012$), with no effect during the cooling phase ($p = 0.123$), and an improvement during the recovery phase ($p = 0.028$). There were no significant changes in the right hand for the AUC. No significant changes were seen between the delta of the left hand versus the delta of the right hand (Table 2).

One year after surgery, the perfusion gradient in the left hand was still improved when compared with the right hand [left delta -0.1 (-32.0–20.6) versus right delta -14.8 (-47.5–4.2), $p = 0.025$], although the variation between patients was high. Heart rate variability showed no differences during the cooling and recovery procedure. Nailfold capillary microscopy also showed no differences between visits for MES, CSURI and PIDL. Furthermore, no differences in PWV were found between visits. Data are presented in Table 2 and Supplemental Tables S1 and S2.

Discussion

We report in the present study, with a limited number of patients with treatment-resistant RP, the one-year follow-up results of unilateral R3 SPTS. Irrespective of the number of patients there is benefit from the procedure on the majority of outcome variables, though some effects seem to attenuate. First, patient-reported outcomes improved significantly, with a remarkable reduction of the duration of the Raynaud's attacks as documented in the Raynaud's diaries. In addition, patients reported less limitations due to improved physical health in conjunction with less pain and enhanced physical functioning, one year after surgery. Consistent with these findings were the effects for the AUC, during the recovery period. The AUC was larger one year after surgery, when compared with baseline, implying a faster return of perfusion following the cooling period. In addition, the perfusion of the left hand is better than before surgery, as indicated by a lower total mean ischaemic time and recovery mean ischaemic time one year after surgery, when compared with baseline. We confirmed that the SPTS procedure did not have any measurable effects on systemic vascular resistance and cardiac sympathetic activity as shown by unchanged pulse wave velocity and heart rate variability, respectively. These findings support the absence of patient-reported systemic adverse events.

Our results are in line with the review of Coveliers et al., reporting beneficial long-term effects (>18 months) in 59% of primary RP patients and in 89% of secondary RP patients, after conventional surgical intervention (sympathectomy) [2]. However, all studies included in this review reported a decrease in effect over time, and symptoms reoccurred in almost all patients. Our study corroborates these previous findings, as indicated by a decline in the initial remarkable improvement of left-hand perfusion after one-year follow-up [6]. Although a decline in some outcomes was observed, the overall beneficial effect on left-hand perfusion remained.

Medical interventions for Raynaud's phenomenon are currently limited. Based on a large amount of evidence Calcium channel blockers are usually prescribed. In severe cases, after failure of first line oral treatment, iloprost infusions and phosphodiesterase-5 (PDE-5) inhibitors may be considered [22–24]. It is important to compare effect size of the SPTS procedure with these conventional treatment strategies. In the reported studies, the baseline number of RP attacks was 14–28 per week (i.e. 2–4 per day). The number of RP attacks was reduced by 2.93 (CI: -3.44–-2.43) through calcium channel blockers [22], by 10.3 (±13.7) and by 12.6 (±12.5), 6 and 9 weeks following iloprost infusion [24]. The daily frequency of attacks was reduced by 0.49 (CI: −0.71–0.28) with PDE-5 inhibitors [23]. To put things into perspective, R3 SPTS reduces the median number of attacks per two weeks by 11 (i.e. from 13 at baseline to 2 one year after the procedure).

As mentioned before, the long-term response to SPTS varies among patients. At this point we can only speculate about the cause of these differences. A possible explanation may be the anatomical variation in the sympathetic innervation of the hand. Encouraged by the success at the R3 level for the treatment of patients with severe palmar hyperhidrosis we decided to use the same level to approach the sympathetic nerves. Though there are rare cases in which R3 SPTS does not suffice, and a more thorough treatment effect is obtained with (redo-surgery and) expansion to the R2 and R4 level. This suggests that for some patients an R3 SPTS alone does not provide a full sympathetic denervation of the hand. Another option to expand sympathetic denervation is digital sympathectomy, especially in patients with non-healing digital ulcers. Another possible explanation may be the difference in the pathogenesis of an attack for primary and secondary Raynaud's. Perhaps unequal results were to be expected following sympathetic denervation of the hand, because sympathetic activity has a larger impact on a primary RP attack, when compared to a secondary RP attack [25].

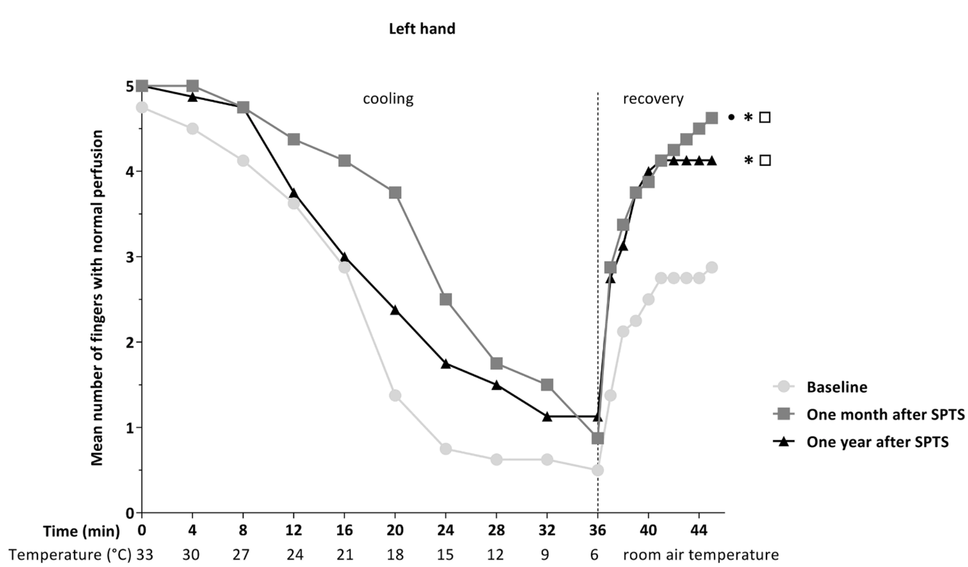

Fig. 1. Cooling and recovery procedure of the left hand before and after left-sided R3 SPTS
Mean number of fingers of the left hand with normal perfusion during the cooling and recovery procedure pre-operatively (baseline), one month post-operatively and one year post-operatively after left-sided R3 SPTS. ●$p<0.05$ for cooling period, *$p<0.05$ for recovery period, □$p<0.05$ for total procedure, all compared to baseline.

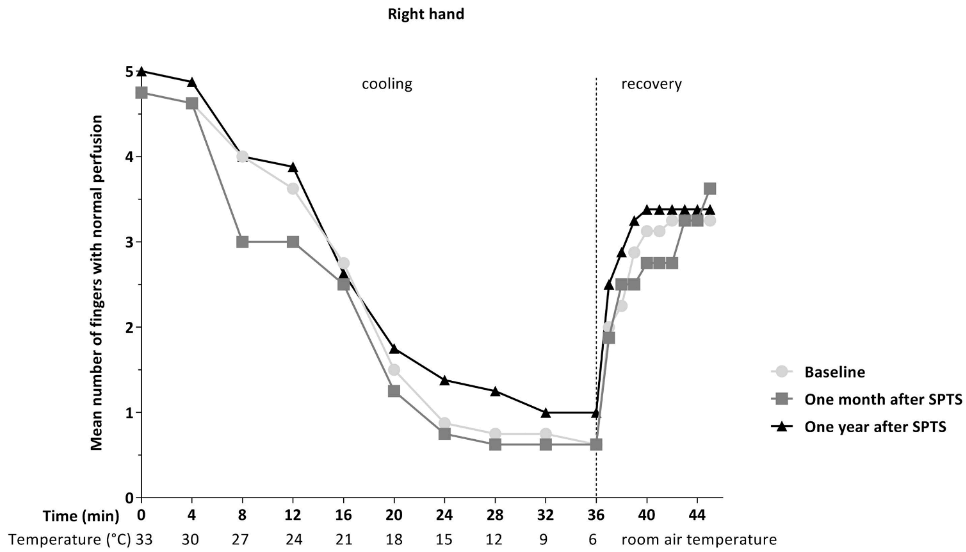

Fig. 2. Cooling and recovery procedure for the right hand before and after left-sided R3 SPTS
Mean number of fingers of the right hand with normal perfusion during the cooling and recovery procedure pre-operatively (baseline), one month post-operatively and one year post-operatively after left-sided R3 SPTS.

Whether patients with severe vascular damage and complications would benefit from this procedure has not been assessed in the current study. Sympathetic activity plays an important role in vasoconstriction, even in patients with structural microvascular damage who have a large disease burden and therefore potentially the greatest clinical benefit [26,27].

Limitations to the study

An obvious limitation of the present study is the small sample size. Only eight patients were included with a large interindividual variation in observed effects. Medical history and underlying etiology of RP varied considerably. Five patients suffered from primary RP, and three patients suffered from RP secondary to connective tissue disease (CTD), i.e. limited cutaneous systemic sclerosis (SSc) ($n = 1$) and mixed connective tissue disease (MCTD) ($n = 2$). Therefore, we were unable to determine the difference in effect of the procedure on primary and secondary RP in this pilot study. Furthermore, there was a large variation in age, RP duration and gender (6 out of 8 were males). Therefore, future studies with a larger sample size should focus on identification of patient characteristics to predict the long-term effects of SPTS more accurate, allowing a better upfront patient selection. Furthermore, objective measurement of treatment effects in RP is challenging, however a prerequisite, due to large interindividual variations, seasonal effects, and patients' perception. The influence of seasonal variation on RP symptom burden, was minimized because baseline and one year measurements were performed around the same time of the year.

We attempted to overcome these limitations by including several Patient Reported Outcome Measures (PROM's) and objective vascular function measurements. In retrospect, Raynaud Condition Score (RP VAS) was not a useful endpoint in this study, because this score focuses on the effect of RP on both hands. However, the RP diary facilitated separate documentation of the left- or right sidedness of symptoms, which indeed showed improvement in the operated left hand. Furthermore, even if symptom relieve occurs only in one of the hands, the overall health related quality of life can be improved. The cooling and recovery procedure is a more accurate method to provoke an attack, however the cold challenge is only limited to the hands and not to the whole body and it took place outside of the daily environment. For future studies, new objective tools are needed, that combine patient reported outcomes with objective measurements of RP attacks on a daily basis. In this study, NCM outcomes were of less importance because NCM patterns change over longer time periods in secondary RP. Longer follow-up is needed to see if SPTS will affect NCM patterns in patients with secondary RP.

The change in LASCA assessed perfusion gradient was remarkably different between the left and right hand. This could potentially be explained by compensational mechanisms in the right hand after sympathicotomy on the left side, but also by difficulties of standardizing the measurement (lack of cold-stimulus, hand and skin aberrations.

Given the above-mentioned interindividual variation with patients as their own controls, this set-up may bias results since ipsilateral SPTS is capable to influence the contralateral side via central nervous system feedback mechanisms. So, a left-sided SPTS procedure may have an additional beneficial effect on the right side. In contrast, it is also conceivable that the body may adapt to the new situation, enabling the left hand to warm up, while the right hand still remains cold. The latter seems unlikely since no alterations were found in measurements representing systemic sympathetic activity (HRV) or systemic vascular resistance (PWV). A randomized, sham-controlled trial may overcome this potential bias, but due to the invasive nature of the SPTS procedure, such a design is deemed unethical.

In conclusion, one year after unilateral R3 SPTS, the duration of the RP attacks was still significantly reduced and patients reported less limitations due to physical health, less pain and physical functioning improved. Furthermore, perfusion of the treated hand remained increased compared to baseline. Though this effect is less obvious one year after surgery as compared to the immediate postoperative period, the treatment effect is relatively stable and durable after one year follow-up. Despite the relatively small study, the high success rate, patient satisfaction (all patients voluntarily opted to undergo R3 SPTS on the right side) and effect stability, R3 SPTS holds promise to be a superior treatment modality, compared to non-surgical treatment options in patients with treatment-resistant RP. A currently on-going study will investigate the five-year follow-up results of bilateral R3 SPTS in a variety of RP patients (NCT04015193).

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Table 2
Vascular measurement outcomes for left (intervention) and right (control) hand and delta (left and right).

	Left Baseline	One month post-operatively	One year post-operatively	Right One month versus baseline(V2–V1)	One year versus baseline(V3–V1)	Baseline	One month post-operatively	One year post-operatively	One month versus baseline(V2–V1)	One year versus baseline(V3–V1)
Mean ischemic time in minutes	23.9 (15.1–29.0)	10.8* (3.3–19.0)	19.6* (5.7–24.8)	−10.4 (−19.9–−3.9)**	−5.0 (−11.5–−2.4)	22.0 (12.0–32.2)	21.8 (15.0–35.9)	22.4 (6.0–30.9)	−0.1 (−4.0–12.1)**	−1.8 (−13.0–2.3)
Mean recovery ischemic time in minutes	5.6 (1.3–9.7)	1.7 (0.1–5.0)*	1.6 (0.4–4.6)*	−3.2 (−6.1–−0.8)**	−1.7 (−5.2–−0.2)	2.6 (1.0–9.7)	3.0 (2.3–8.0)	3.0 (1.0–7.8)	0.0 (−0.3–1.7)**	−1.0 (−2.5–0.3)
AUC cooling	91 (56–101)	130 (102–155)*	88 (68–149)	−7.7 (−9.0–−1.8) **	−0.6 (−6.8–3.6)	90 (48–118)	84 (32–111)	84 (55–149)	0.7 (−2.4–8.2)**	−3.3 (−8.2–4.2)
AUC recovery	21 (1–41)	38 (22–43)*	38 (24–43)*	42 (29–68)**	26 (−17–54)	34 (2–42)	32 (9–35)	35 (11–42)	10 (−61–22)**	9 (−28–65)
AUC total	101 (75–140)	166 (122–197)*	118 (95–190)*	12 [1]– 24)**	5 (0–22)	109 (60–160)	109 (40–143)	106 (65–190)	−1 (−8–1)**	3 (−1–8)
Mean temperature of loss of perfusion in °C	19.6 (17.1–23.3)	16.2 (12.0–17.0)	19.0 (18.0–21.6)	−7.7 (−9–−1.8)*	−0.6 (−6.8–3.6)	18.8 (17.6–24.5)	21.3 (17.4–26.9)	20.2 (11.9–23.3)	0.7 (−2.4–8.2)*	−3.3 (−8.2–4.2)
Perfusion gradient in perfusion units ROI 1–ROI 3	21.1 (−5.1–40.1)	29.3 (18.1–43.2)	16.7 (−3.5–35.8)	14.0 (0.2–27.2)**	−0.1 (−32.0–20.6)**	25.6 (−9.8–48.4)	4.4 (−3.8–28.2)	−2.5 (−8.9–1.5)	−15.5 (−35.3–12.0)**	−14.8 (−47.5–4.2)**
Carotid femoral PWV	6.5 (5.3–8.3)	6.8 (5.4–7.9)	6.2 (5.5–7.7)	−0.08 (−0.8–0.7)	−0.3 (−1.3–0.8)	7.0 (5.6–7.7)	6.6 (5.1–7.2)	6.0 (5.6–7.6)	−0.05 (−1.1–0.1)	−0.6 (−1.0–−0.1)

Data one month post-operatively is shown to compare with one year post-operatively, data was already published before in van Roon et al. [6].
*$p < 0.05$ between visit and baseline.
**$p < 0.05$ between delta of left and right hand, AUC = Area Under the Curve, ROI = Region of Interest, PWV = Pulse Wave Velocity.

Declaration of Competing Interest

The authors have declared no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152065.

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