Cardiac Autonomic Changes After Thoracic Sympathectomy: A Prospective, Randomized Study

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Background. **We evaluated whether cardiac autonomic changes could be associated with different extent of sympathetic nerve resection in the management of essential palmar hyperhidrosis.**

Methods. **Sixty patients with essential palmar hyperhidrosis were randomly allocated to undergo excision of T3 ganglia (sympathicectomy group; n = 30) or to interruption of sympathetic chain at the T2 to T3 level with ganglion sparing (sympathicotomy group; n = 30). Time and frequency domains were measured with a 24-Holter monitor during daytime, nighttime, and 24-hour periods at different interval points (7 days before operation; 24 hours; and 1, 3, and 6 months later), and the differences were statistically compared. Clinical outcomes were also evaluated.**

Results. **Twenty-eight of 30 patients of the sympathectomy and 29 of 30 patients of the sympathicotomy group completed the study. In both groups, we observed a significant increase ($p < 0.05$) of vagal activity measurements as root mean square of the successive differences of heart period; proportion of adjacent normal R-R intervals >50 ms; high frequency; and a significant decrease ($p < 0.05$) of adrenergic activity variables as heart rate, low frequency, and the ratio between low frequency and high frequency during daytime, nighttime, and 24-hour periods. These changes were significantly more evident ($p < 0.05$) in the sympathectomy group than in the sympathicotomy group. Clinical outcomes were similar between the two groups.**

Conclusions. **Endoscopic thoracic sympathectomy caused a shift of sympathovagal balance toward parasympathetic tone that seems to be associated with the extent of denervation. This trial was registered at clinicaltrials.gov as NCT02733497.**

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Essential palmar hyperhidrosis (EPH) is a pathologic condition of excessive sweating of the hands due to an unexplained overactivity of the T2 and T3 sympathetic fibers. Endoscopy thoracoscopic sympathectomy (ETS) is the treatment of choice in patients with EPH refractory to medical treatment [1, 2].

Heart rate variability (HRV) is a simple and noninvasive method based on electrocardiogram to evaluate the sympathovagal balance at the sinoatrial level [3]. Several studies have found that ETS caused a decrease of heart rate (HR), an increase of HRV, and a shift of sympathovagal balance toward parasympathetic tone [4–9], but it remains unclear if these changes are associated with the extent of denervation.

Thus, in the present study we performed a prospective analysis of HRV function in patients with EPH undergoing different grades of sympathetic denervations with the hypothesis that reducing the extent of sympathetic nerve resection will result in reducing cardiac autonomic changes.

Material and Methods

Study Design

This was an unicenter prospective study performed at the Thoracic Surgery Unit of Second University of Naples. Patients with severe EPH were randomly assigned to the sympathectomy or sympathicotomy group, and no changes to methods as type of randomization or eligibility criteria were attended after study commencement. The study design, planned according to the Consolidated Standards of Reporting Trials (CONSORT) guideline [10], was approved by the Ethical Committee of Second University of Naples (code number 1185/2011) and registered at ClinicalTrials.gov as NCT02733497.

Participants

All consecutive patients aged older than 18 years and scheduled for bilateral ETS for management of severe

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EPH between January 2012 and September 2014 were eligible. Exclusion criteria were (1) any contraindications for general anaesthesia, selective endotracheal intubation, or both; (2) previous pleural or lung diseases; (3) cardiac diseases, taking medications with cardiac-related effects, or both; (4) secondary hyperhidrosis; (5) mild or moderate palmar hyperhidrosis for which less-invasive procedures than an operation are indicated; and (6) hyperhidrosis present in other part of the body (ie, palmar and axillar hyperhidrosis).

The patients were scheduled for an operation after failure of medical therapy. A preoperative complete consultation was performed to evaluate personal, professional, and social handicaps related to palmar hyperhidrosis. All patients underwent a preoperative chest x-ray film and detailed cardiac evaluation to exclude lung, pleural, and cardiac diseases. Pros and cons of the ETS were explained to patients who were aware that (1) both procedures (sympathectomy and sympathicotomy) were equally effective and had similar complication rates as reported by data in the literature, (2) their participation was voluntary, and (3) they might withdraw consent to participate at any time during the study without any consequences for their care. All patients gave a written informed consent before entering the study.

Interventions

Bilateral ETSs were performed in a one-stage procedure by the same surgeon under general anesthesia and selective ventilation. Patient was placed in standard lateral thoracotomy position [11]; the procedure was performed with two ports: a 10-mm port in the posterior-axillary line at the third intercostal space for the introduction of telescope, and a 5-mm port in the anterior axillary line at the third intercostal space for working instruments. After identification of sympathetic chain, the T3 ganglion was excised at the top of the third rib or the sympathetic chain was resected between T2 and T3 ganglia with T3 ganglion sparing if patients were allocated in the sympathectomy or sympathicotomy group, respectively. At the end of the procedure, a temporary 16F drainage was inserted into the thoracic cavity through the camera port and connected to a water seal system. After re-inflating the lung, the tube was quickly removed, and the incision was closed.

Primary End Point

The primary end point was to evaluate whether the changes in HRV could be associated with the extent of sympathetic resection. In each group, HRV was evaluated 7 day before ETS and 24 hours and 1, 3, and 6 months later, using a 24-hour Holter recording.

HOLTER RECORDINGS. A seven-lead 24-hour electrocardiogram (ECG) holter (CardioVex Holter MMC10D; Juramento 5841-(1431) Bs. As. Argentina) was used. Recordings started systematically at 4 PM. Subjects were asked to not perform intense exercise and to have a routine daily activity during the recording. Recordings less than 20 hours of analyzable data were excluded. The 24 hours were digitalized on KL software (KL Software, New York, NY). The tapes were manually reviewed, and the operator was blinded regarding the group. Each variable was analyzed for three periods as follows: daytime (from 6 AM to 10 PM), nighttime (from 10 PM to 6 AM), and the entire 24 hours. The data were then analyzed with dedicated software that provided measurements of HRV within the time and the frequency domains as summarized in Table 1.

TIME DOMAIN MEASUREMENTS. Time domain analysis measuresd the changes in HR with time or the intervals between successive normal cardiac cycles. From a continuous ECG recording 24-hour Holter, each QRS complex was detected, and the normal R-R intervals (NNs) from sinus depolarizations, or the instantaneous HR, was then determinated. Time domain analysis included standard deviation (SD) of the NN (SDNN), SD of all 5-minute mean NNs (SDANN), the root mean square of difference of successive NNs (RMSSD), and the proportion of adjacent NNs greater than 50 ms (pNN50). SDNN and SDANN are global indexes of HRV and reflect its day/night changes. RMSSD and pNN50 reflect alterations in autonomic rate that are predominantly vagally mediated and are not affected by day/night variations. All time domain measurements were evaluated in 24-hour periods and were expressed in milliseconds, except the pNN50 that is expressed as a percentage.

FREQUENCY DOMAIN MEASUREMENTS OF HRV. Frequency domain, also called power spectrum analysis, provides information on the amount of the intensity (power) in the

Table 1. Time and the Frequency Domains of Heart Rate Variability

Domain	Variable	Description	Regulation
Time	NN	Normal R-R interval	Vagal activity
	SDNN	Standard deviation of normal R-R interval	Circadian rhythms
	SDANN	Standard deviation of all 5-minute mean normal R-R intervals	Circadian rhythms
	RMSSD	Root mean square of difference of successive normal R-R intervals	Vagal activity
	pNN50	Proportion of adjacent normal R-R intervals >50 ms	Vagal activity
Frequency	HF	High-frequency band (0.15–0.40 Hz)	Vagal activity
	HFnu	Normalization of high-frequency band	Vagal activity
	LF	Low-frequency band (0.04–0.5 Hz)	Sympathetic activity
	LFnu	Normalization of low-frequency band	Sympathetic activity
	LF/HF	Ratio of high-frequency to low-frequency band	Sympathovagal balance