Abnormal modulation of electrodermal activity by thermoalgesic stimuli in patients with primary palmar hyperhidrosis

Pedro Schestatsky, Marco A Callejas, Josep Valls-Solé

ABSTRACT
Background The authors examined the effects of thermal stimulation on electrodermal activity (EDA) in patients with primary palmar hyperhidrosis (PPH). The authors hypothesised that temperature changes may induce abnormal sudomotor reactions because of simultaneous activation of sudomotor centres through thermal and emotional pathways, and compared patients before and after thoracoscopic sympathectomy.

Methods The authors studied 18 PPH patients and 20 controls. Patients reported subjective evaluation of their symptoms using a visual analogue scale for palmar sweating and for body sweating (bs-VAS). The authors applied focal thermal stimulation to quantify sensory perception and measure ongoing changes in EDA recorded from the palm of the hands.

Results Before sympathectomy, patients had lower sensory perception thresholds and higher EDA levels than controls. Increased EDA occurred along the whole test, with no significant modulation by changes in thermal stimulation. Sensory perception normalised after sympathectomy, but thermal modulation of EDA remained abnormal whenever sudomotor activity was present after surgery. There was a significant positive correlation between EDA levels before treatment and the bs-VAS (from r=0.45 to r=0.57).

Conclusions Patients with PPH show perceptual abnormalities and exaggerated sudomotor reactions to thermoalgesic stimulation, consistent with central sensitisation of sympathetic circuits. The reduced sympathetic outflow after thoracoscopic sympathectomy induced normalisation of sensory perception, but it did not modify the abnormal control of efferent sudomotor activity.

INTRODUCTION
Primary palmar hyperhidrosis (PPH) involves excessive sweating of the hands with no identifiable cause.\(^1\)\(^2\) Despite its prevalence and impact on quality of life, physiological mechanisms underlying PPH remain poorly understood.\(^3\) The analysis of sudomotor skin response has shed some light on the wide range of axons responding to electrical stimuli. Second, there is increasing evidence that brainstem autonomic centres, which contribute to the control of sudomotor activity, respond to thermoalgesic stimuli.\(^4\)\(^5\)\(^6\) Third, thermal stimulation allows for on-line modulation of intensity, which helps to diminish the surprise effect of the sudden, phasic electrical stimulation and permits recording the changes induced in EDA before, during and after stimulation.\(^7\)

In the study reported here, we analysed the changes in EDA induced by slow rising thermal stimulation of the skin at forearm level in patients with PPH before and after thoracoscopic sympathectomy. We further assessed thermal thresholds in the upper limbs of these patients to assess the possible correlation of these results with temperature-related C fibre function.

METHODS
The study was performed in 21 patients with PPH (10 women, eight men, aged 25–45 years old), recruited consecutively among those attending our clinic during the 6 months period January to June 2007. We also studied 20 healthy subjects, recruited among the spouses of the patients and colleagues to match for age and sex with those of the patients (10 women, 10 men, aged 24–46 years old). No healthy subject or patient was under chronic medication regime or had any health condition known to affect the peripheral and autonomic nervous system functions or thermoalgesic perception. The evaluation was performed in a quiet, partially dark room, at a temperature between 23.0°C and 24.0°C. All subjects gave written informed consent for the study, which was designed in accordance with the Helsinki Declaration and approved by the Ethical Committee of the Hospital Clinic of Barcelona.

Thoracoscopic sympathectomy
After general anaesthesia, a videothoracoscopic catheter was introduced through a trocar inserted in the axillary region. The second thoracic ganglion (T2) was identified, usually in the space between the second and third ribs. The sympathetic trunk was severed at this level, trying to isolate T2 and T3 ganglia, as performed in previous studies from our group.\(^2\)\(^3\)\(^4\)\(^6\) The operation was carried out bilaterally, during the same surgical procedure.

Clinical interview
Interviews were carried out before and after thoracoscopic sympathectomy. PPH patients were
asked how much the excessive sweating interfered with their routine activities of daily living by using a 10 cm visual analogue scale (VAS). The assessment was requested separately for the palms of the hands (palm sweating, ps-VAS) and for the rest of the body (body sweating, bs-VAS). The scales spanned from 0=no interference to 10=high interference with daily living. Clinical interview and tests were performed between 10 and 45 days before and 10 and 50 days after surgery. All studies were performed always at the same time of the day (early afternoon) by a single experimenter (PS), blinded for the clinical status of subjects.

Thermolgesic stimulation
All temperature-related stimuli were applied with a Peltier-type contact rectangular thermode from a Thermodest (Somedic, Sweden), with a stimulating area of 12.5 cm². The thermode was attached with a velcro strip to the ventral aspect of the subject’s mid forearm region. We first determined warm and heat pain thresholds using the method of limits. This was considered the mean of three consecutive stimuli. Individual thresholds were used to determine the peak of the temperature stimuli to apply to that particular individual (see below).

Experimental procedure
Subjects were sitting on a comfortable chair. The Peltier thermode was attached to the distal ventral side of their forearm. We used thermal stimuli with ramp rates of 0.5°C/s to a peak temperature intensity of 120% of the individual’s pain threshold. We performed three trials on each side, with an interval of at least 20 min between two consecutive trials. Subjects were asked to describe their subjective sensory perception using a 10 cm long linear analogue potentiometer (RSA001159002, Alps, Germany) installed in a metallic box and provided with a lever. We marked seven labels on the side of the lever: ‘no temperature sensation,’ ‘light warm,’ ‘medium warm,’ ‘high warm,’ ‘light pain,’ ‘medium pain’ and ‘high pain.’ Subjects were instructed to be ready to move the lever with their right hand as soon as they felt any change in temperature, and keep marking the changes in the intensity of their sensations until the stimulation was over. The lever could be moved without resistance along its course, and the use of intermediate positions was encouraged. Signals from the lever (perception signals) were recorded together with the temperature signal generated by the Thermodest during the entire trial. They were digitised at a sampling frequency of 200 Hz and fed into a computer equipped with a software for off-line analysis (Acknowledge, Bionics Systems, Bionic Iberica, Barcelona, Spain).

Electrodermal activity
EDA was continuously monitored from 10 s before to 10 s after thermolgesic stimulation through surface silver/silver chloride 9-mm-diameter recording electrodes attached to the skin of the palm (active) and dorsum (reference) of the subject’s hands. We assumed that there was a significant change in EDA when there was a negative or positive shift of the baseline level with an amplitude of at least 100 µV and a duration of at least 0.5 s. The signal was preamplified at a gain of 0.5 mV using a Nihon-Kohden Neuropack-8 electromyograph (Nihon-Kohden, London). The output signal from the electromyograph was digitised with a band-pass frequency filter set at 0.1–100 Hz.

Data reduction and statistical analysis
The onset of temperature change was considered time 0 (independent variable). In order to correlate sensory perception with EDA, we determined three time points in the sensory perception signal: (1) warm onset, as the time at which subjects marked their first perception of ‘light warm’; (2) pain onset, as the time when subjects marked perception of ‘light pain’; and (5) peak of maximum sensation, as the time at which subjects reached their highest individual score. The highest individual score was defined as the percentage of the maximum possible lever displacement. This divided the sensory perception into four different segments: (1) the ‘preperception phase,’ spanning from the beginning of recording (5 s before time 0) to warm onset; (2) the ‘warm phase,’ spanning from warm onset to pain onset; (3) the ‘pain phase,’ spanning from pain onset to the time in which subjects returned the tp-VAS lever to values lower than ‘light pain’; and (4) the ‘postperception phase,’ spanning from the end of the ‘pain phase’ until 5 s after the end of the stimulation. The temperature of the thermode was noted at each event. However, for the statistical analysis, we only considered ‘light warm’ and ‘light pain’ latency values (warm and heat pain thresholds, respectively).

EDA was analysed according to the sensory perception phases (figure 1). Individual absolute EDA was calculated for each phase as the area under the curve, given in microvolts multiplied by phase duration (absolute EDA, a-EDA). In addition, because of the expected large interindividual differences in background EDA, statistical analyses were also done on normalised EDA (n-EDA), obtained by expressing the area of each phase as percentages of the individual’s mean value calculated in the preperception phase for each condition. Because none of our patients had asymmetrical sweating, and no differences between sides were expected either in sudomotor activity or in thermal thresholds, data from both sides were pooled together. Normality of distribution of the data was assessed using the Kolmogorov–Smirnov test. For descriptive statistics of quantitative data, we report the mean and SD values. The Student t test and χ² test were used for comparison of demographic and clinical data between patients and controls.

For comparisons between the three groups (controls, PPH before thoracoscopic sympathectomy and PPH after thoracoscopic sympathectomy) we used repeated-measures ANOVA. We also examined whether EDA values were different in each phase in the same individual, using one-way ANOVA, after pooling data for all conditions. The Bonferroni test was used for post-hoc analyses when significant differences were found. Finally, we examined the possible correlation between the amount of EDA in each sensory perception phase with the ps-VAS...
perception pattern of patients in comparison with control temperature. There were noticeable differences in the sensory drop to baseline values, which was faster than the drop in a mean temperature of 42.3 ± 9.4 °C, while their perception remained mostly unchanged for a mean of 6 ± 6 s, giving rise to a relatively flat segment between warm and pain sensations. The mean slope between 38°C and 42°C was 0.02 ± 0.005°C/s in healthy subjects and 0.09 ± 0.03°C/s in patients before sympathectomy. This value showed a tendency to normalisation after surgery, with a mean of 0.06 ± 0.008°C/s.

The mean a-EDA was higher in patients than in control subjects in all phases (one-way ANOVA; p<0.01 for all comparisons). In healthy subjects, EDA varied systematically according to the sensory perception phases. The statistical comparison between the four phases on n-EDA (normalised as percentage of the prestimulation phase) showed significant differences (ANOVA; p<0.05), which were due to a higher n-EDA in the pain phase and lower n-EDA in the poststimulation phase in comparison with the n-EDA in the prestimulation phase (100%). In contrast, PPH patients before sympathectomy showed an absence of phase-related changes in EDA. Figure 4 shows the mean and SD values for n-EDA in all subjects groups for all sensory perception phases. A striking difference between patients and control subjects was the absence in patients of a marked decrease in EDA after the pain-sensation phase (figures 3 and 4). Table 2 summarises the mean and SD values for a-EDA and n-EDA for each phase in control subjects and patients.

Finally, we found a positive correlation between the mean level of pretreatment a-EDA and bs-VAS (r=0.45 to 0.57; p<0.01). No significant correlation was found between ps-VAS and bs-VAS before sympathectomy (Bonferroni test; p>0.001 for all comparisons). There were no differences between patients after sympathectomy and controls (Bonferroni test; p=0.2). Table 1 displays thermal thresholds of all subjects groups. Differences were also observed in the mean slope of the relatively flat segment between warm and pain sensations. The mean slope between 38°C and 42°C was 0.02 ± 0.005°C/s in healthy subjects and 0.09 ± 0.03°C/s in patients before sympathectomy. This value showed a tendency to normalisation after surgery, with a mean of 0.06 ± 0.008°C/s.

The main findings of our study are: (1) temperature-induced EDA is higher in patients with PPH than in controls, suggesting an abnormal effect of temperature inputs on autonomic centres; (2) perception of warm sensation is altered in PPH patients, suggesting sensitisation in the temperature perception pathway; and (3) there was a significant positive correlation between temperature-induced EDA and the magnitude of bs-VAS after treatment.

Figure 2 Self-perception of sweating in the palms (ps-VAS) and body (bs-VAS). The size of the bars represents the mean, and the length of the wisker represents SD, obtained from patients with primary palmar hyperhidrosis before and after surgery. Note the significant decrease in ps-VAS and increase in bs-VAS after the procedure.

Figure 3 Temperature stimulation (temp), sensory perception (percept) and electrodermal activity (EDA) recorded from a single representative subject from each group: control subjects (A), patients with primary palmar hyperhidrosis (PPH) before (B) and after sympathectomy (C). The tilted arrow in B points to the more pronounced slope of sensory perception in patients before surgery. The horizontal line and asterisk in control subjects point to the segment of quiet EDA after the peak of the stimulus. Note the absence of such a segment in patients, a situation that did not change after sympathectomy.

Table 2 summarises the mean and SD values for a-EDA and bs-VAS using the Pearson correlation coefficient. A value of p<0.05 was considered to indicate statistical significance.

RESULTS
Out of the initial 21 patients recruited for the study, three were lost during follow-up after thoracoscopic sympathectomy for various reasons. Therefore, 18 patients were fully evaluated in both sessions. There were no differences between patients and control subjects with regard to sex ($\chi^2$; p>0.05), age, weight and height (ANOVA; p>0.05 for all comparisons). After sympathectomy, all patients reported a remarkable improvement of palmar hyperhidrosis (PPH) before (B) and (2) beyond this point, (3) then, at period; (3) there was a significant increase in the mean slope of the relatively flat segment in patients, a situation suggesting sensitisation in the temperature perception pathway; and (4) there was a fast drop to baseline values, which was faster than the drop in temperature. There were noticeable differences in the sensory perception phases. A striking difference between patients and control subjects was the absence in patients of a marked decrease in EDA after the pain-sensation phase (figures 3 and 4). Table 2 summarises the mean and SD values for a-EDA and n-EDA for each phase in control subjects and patients.

DISCUSSION
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The finding of an increased activity in sudomotor pathways in patients with PPH is not new. Several authors have reported abnormalities of the sudomotor skin responses\textsuperscript{5,19} and skin conductance level,\textsuperscript{6} other than those just related to the expected increase in the amount of sweating. Manca et al\textsuperscript{6} applied pairs of electrical stimuli in the median nerve separated by increasing interstimulus intervals (ISI). The authors found that patients recovered the sudomotor excitability with lower ISIs in comparison with controls. In the same line, Lladó et al\textsuperscript{19} observed a higher prevalence of double peak sudomotor potentials in response to single electrical stimuli. Additionally, Chen et al\textsuperscript{2} and Lefaucheur et al\textsuperscript{19} found various abnormalities, including a higher occurrence of absent sudomotor responses, which were interpreted as indicative of ‘excessively busy’ sweat glands. Such abnormalities persisted after thoracoscopic sympathectomy,\textsuperscript{5} pointing out to a hyper-excitability of the somato-sympathetic circuits as a basic pathophysiological mechanism of PPH. As in previously published studies, we found that sudomotor activity was significantly reduced after sympathectomy. However, reflex sudomotor responses recorded with electrophysiological methods were still present in most of our patients. This could be due to unintended incompleteness of the sympathetic lesion. Thermal stimulation could have been a relatively strong one to cause activation of the remaining sympathetic circuits because of the coincidence of the stimulation activating both thermoregulatory and emotional sweating simultaneously.\textsuperscript{17} Although the two forms of sweating might have different and independent control mechanisms and central drives,\textsuperscript{17,20} thermal stimulation might have accessed the two circuits and induce a stronger output signal from sudomotor centres. A more efficient activation of the autonomic centres by thermal stimulation could explain why most responses were still present after sympathectomy, which is different from what has been reported with other types of stimulation.\textsuperscript{5,19}

PPH patients had lower thresholds to warm stimuli compared with control subjects. This finding is in accordance with the observations reported by Schlereth et al\textsuperscript{2} who showed that acetylcholine sensitises C afferent fibres and decrease thermal thresholds in normal subjects. In fact, there is convincing evidence that sympathetic postganglionic axons, which are hyperactive in PPH patients, excite primary afferent axons by activating alpha-adrenoceptors and generating activity in the ‘nociceptive pathway,’ which conveys warm and pain information up to the central nervous system.\textsuperscript{32–34} A similar mechanism has been hypothesised to explain the analgesic effect of botulinum toxin,\textsuperscript{25} in which case reduced acetylcholine liberation would decrease C fibres sensitivity. Our patients did not have clinical (ie, pain or dysaesthesias) or neurophysiological signs (ie, higher thermal thresholds) of small fibre disease, as observed in patients with diabetes with painful sensory neuropathy.\textsuperscript{26} Therefore, our findings suggest that, apart from nerve injury, C afferent fibres can be sensitised by ongoing primary autonomic activity. For instance, patients with complex regional pain syndrome type I are more sensitive than healthy subjects to temperature stimuli, and sympathetic activity has been proposed as an effective treatment for such patients.\textsuperscript{27–29}

EDA reflects more than simply sweating activity. For example, sudomotor responses were present despite reduced skin sympathetic nerve activity and complete absence of sweating in an anhydrotic female carrier of Fabry’s disease.\textsuperscript{30} In addition, sympathectomy does not significantly affect the central nervous system abnormality underlying hyperexcitability of the somato-sympathetic sudomotor circuit at short term.\textsuperscript{6} PPH patients might actually have a dysfunction in the autonomic centres of the brainstem that are both responsible for inhibition of sensory perception and peripheral autonomic activity. This hypothesis would explain lower thermal thresholds and higher autonomic responses of our PPH patients compared with normal subjects. It is also possible that the dysfunction resides at the cortical level, since the frontal or anterior cingulate cortex are prominently

### Table 1 Psychophysical parameters measured in control subjects and patients with primary palmar hyperhidrosis before and after thoracoscopic sympathectomy

<table>
<thead>
<tr>
<th>Thermoalgesic thresholds</th>
<th>Control subjects (n = 20)</th>
<th>Primary palmar hyperhidrosis patients (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>thermoalgesic to pain (°C)</td>
<td>thermoalgesic to pain (°C)</td>
</tr>
<tr>
<td>Warm</td>
<td>33.9 (1.9)</td>
<td>30.4 (1.3)</td>
</tr>
<tr>
<td>Heat pain</td>
<td>42.2 (1.2)</td>
<td>42.5 (0.9)</td>
</tr>
</tbody>
</table>

Note: NS, non-significant; PPH, primary palmar hyperhidrosis; TS, thoracoscopic sympathectomy.

### Table 2 Neurophysiological parameters of controls and patients with primary palmar hyperhidrosis before and after thoracoscopic sympathectomy

<table>
<thead>
<tr>
<th>Phase</th>
<th>Control subjects</th>
<th>Primary palmar hyperhidrosis patients (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a-EDA</td>
<td>n-EDA</td>
</tr>
<tr>
<td></td>
<td>(µV/s)</td>
<td>(%)</td>
</tr>
<tr>
<td>Pre</td>
<td>117 (5.0)</td>
<td>100.00</td>
</tr>
<tr>
<td>Warm</td>
<td>159 (6.8)</td>
<td>136.0 (15.0)</td>
</tr>
<tr>
<td>Pain</td>
<td>196 (8.4)</td>
<td>168.3 (13.2)</td>
</tr>
<tr>
<td>Post</td>
<td>73 (3.1)</td>
<td>62.8 (8.9)</td>
</tr>
</tbody>
</table>

Note: a-EDA, absolute electrodermal activity (µV/s); n-EDA, normalised electrodermal activity, given as a percentage of the a-EDA mean value calculated in the prestimulation phase.
involved in the control of emotional sweating.\textsuperscript{31} In the same line, Fredrikson and colleagues\textsuperscript{22} observed that electrical stimulation at the thalamus, anterior cingulate and frontal cortex is able to modulate the sympathetic skin responses, and functional imaging studies have shown a positive correlation of sympathetic skin responses with neural activity in these areas in subjects experiencing emotional stimuli.\textsuperscript{32} At the subcortical level, the thalamus would be another candidate for mediating hyperhidrosis in certain conditions. Indeed, a misplaced electrode for deep brain stimulation was recently implicated in iatrogenic hyperhidrosis.\textsuperscript{33}

Our study has several limitations. First, one could argue that higher sudomotor activity and lower thresholds can also indicate a state of hypervigilance in patients with anxiety disorder. Although we did not assess anxiety symptoms, our patients were not under psychiatric treatment or using psychotropic drugs. Furthermore, no direct association between anxiety scores and hyperhidrosis was found in recent studies.\textsuperscript{34} 35 Second, we did not use objective tools for analysing the nociceptive pathway such as nociceptive evoked potentials. However, the data on thermal thresholds were very reproducible within subjects. Third, we did not use sudomotor techniques that evaluate the peripheral autonomic pathway selectively and precisely, that is, QSART or silicone impressions.\textsuperscript{17 36 37} Actually, changes in EDA reflect activity in a polysynaptic reflex circuit that includes central and peripheral components, and the use of QSART could have allowed us to separate the effects of thoracic sympathectomy in both parts of the autonomic system.

We had a relatively small sample of patients. However, our findings were very consistent and reproducible. Thermal stimulation seems to provide meaningful results in the study of skin autonomic function in PPH patients. Our patients showed different and consistent phases of the ongoing sudomotor responses that could offer new possibilities for clinical and research purposes. For instance, the lack of EDA silent period observed in our patients was a new feature of PPH that has been detected by using slowly rising and falling thermal stimuli over the skin. Apart from that, it seems that the temperature-induced EDA of PPH patients was a good predictor of compensatory sweating in short-term follow-up after sympathectomy. More studies are justified in the future using combination of various natural stimuli and recording techniques to expand our knowledge on the pathophysiological mechanisms of PPH.

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Competing interests None.

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