Cardiac Autonomic Function in Patients Suffering from Primary Focal Hyperhidrosis

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\textbf{Key Words}
Power spectral analysis · Heart rate variability · Hyperhidrosis, primary focal · Autonomic nervous system

\textbf{Abstract}
Cardiac autonomic function in patients (n = 63) with primary focal hyperhidrosis and healthy controls (n = 28) was investigated by short-term frequency domain power spectral analysis of heart rate variability. The power of the very-low-frequency band (0.01–0.05 Hz) was significantly lower in patients with axillary hyperhidrosis than in controls. No differences between groups could be observed at investigation of the low-frequency band (0.05–0.15 Hz), which was a surprising finding because this band represents also sympathetic cardiac innervation. At the high-frequency band (0.15–0.5 Hz), which represents parasympathetic cardiac innervation, an interaction of type and position influencing spectral power was detected. Our highly interesting findings indicate that primary focal hyperhidrosis is based on a much more complex autonomic dysfunction than generalised sympathetic overactivity and seems to involve the parasympathetic nervous system as well.

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\textbf{Introduction}

Primary focal hyperhidrosis is a dysfunction of the autonomic nervous system that usually manifests early in adolescence and has to be distinguished from hyperhidrosis because of endocrinological abnormalities, inflammatory conditions and cerebrovascular diseases [1]. Typical locations of excessive sweating are the axillary, palmar and plantar and axillolapalmar regions [2]. Hyperhidrosis is a socially and emotionally disturbing condition [3] which severely reduces quality of life [4]. Therapeutic approaches include sympathectomy, local application of aluminum chloride, iontophoresis and local injections of botulinum A toxin [4–7]. The aetiology of this disturbance is unknown [8, 9], but the definition of autonomic abnormalities in primary focal hyperhidrosis is of paramount importance due to the clinical and social relevance of this disease. To our knowledge, very few data are available on autonomic function in primary focal hyperhidrosis [1, 9–11]. Previous studies showed that cardiac autonomic function is altered in patients suffering from primary hyperhidrosis compared to healthy subjects [9, 11]. These findings suggest that primary focal hyperhidrosis is not only a local disturbance, but results from general dysfunction of the autonomic nervous system, also involving cardiac autonomic control.
The aim of our study was to investigate the cardiac autonomic function of patients suffering from different types of primary focal hyperhidrosis with short-term power spectral analysis of heart rate variability (HRV) compared to healthy controls.

Short-term power spectral analysis of HRV is a non-invasive method for quantitative assessment of cardiovascular autonomic regulatory responses [12, 13]. This method is based on RR interval fluctuations in the heart rate record, and by the means of fast Fourier transformation, three main spectral components may be distinguished: very low, low, and high-frequency bands [13].

Mechanisms and origins of very low frequencies (0.01–0.05 Hz) are not sufficiently delineated yet [14]. The power of low frequencies (0.05–0.15 Hz) is said to represent a complex combination of sympathetic and parasympathetic effects on cardiac autonomic function [14]. High frequencies (0.15–0.5 Hz) are mediated primarily by vagal innervation of the heart [14]. In the past years, power spectral analysis of HRV has been mainly used in cardiology [15] and to investigate diabetic neuropathy [13, 16], but it is also used increasingly in psychiatric [17–20] and neurological research [21–24].

Subjects and Methods

Subjects

We investigated 83 patients suffering from primary focal hyperhidrosis: 25 patients with isolated axillary hyperhidrosis (12 male, 13 female; mean age 33.5 ± 9 years), 12 with palmar/plantar hyperhidrosis (6 male, 6 female; mean age 32.6 ± 12.2 years), and 26 patients with axillar/palmar/plantar hyperhidrosis (12 male, 14 female; mean age 30.1 ± 8.3 years). As control group, we investigated 28 normal subjects (14 male, 14 female; mean age 30.7 ± 6.2 years).

All patients were recruited from our outpatient department where they were referred to because of socially handicapping focal hyperhidrosis, resistant to conventional treatment (astringents and local antiperspirants containing aluminum salts). Patients were investigated anamnestically as well as neurologically, and X-ray investigation of the chest and blood analysis were performed. Primary focal hyperhidrosis was diagnosed when patients suffered from hyperhidrosis restricted to axillary, palmar/plantar or axillar/palmar/plantar regions for longer than 6 months, neurological status was normal, and no evidence of systemic diseases that may cause hyperhidrosis (e.g., diabetes or thyroidal dysfunction) was found. Diagnosis of focal hyperhidrosis was confirmed by nialminidrin sweat test [25] on the hyperhidrotic regions. We excluded subjects younger than 19 years of age, patients with drug-induced focal hyperhidrosis [26], subjects with regular medication which could possibly influence heart rate, and patients with any history of cardiac diseases or arrhythmia. Informed consent to power spectral analysis was obtained from all patients after a full oral explanation.

Procedure

Investigations always took place in the same room at a constant temperature of 22°C and minimisation of arousal stimuli between 11 a.m. and 4 p.m. After a resting period of at least 15 min, three consecutive examination positions were used in a modified orthostatic test: supine 1, standing, and supine 2 [27]. This twofold change of posture is considered an important provocation of both branches of the autonomic nervous system [28].

Subjects were instructed to breathe regularly with a frequency of 15 breaths/min. Frequency domain short-term power spectral analysis of HRV was performed, using a Variapulse TF 3 system (Simac Medi, Czech Republic) with a resolution time of 1 ms [27, 29]. The computational method was based on the fast Fourier transformation modified by algorithm of coarse-graining spectral analysis [30]. In this method, non-harmonic elements are removed from the lower frequency bands (1/f), emphasising only the harmonic components [30]. Artefacts were filtered automatically and manually, calculations being made for a 256-second artefact-free window for each position.

We measured absolute values of power in μV² [31] of the very-low (0.01–0.05 Hz), the low (0.05–0.15 Hz)-, and the high (0.15–0.5 Hz)-frequency bands. Standard deviations were calculated for each parameter and findings bearing more than 35% relative standard deviation within any of the positions, suggesting nonstationarity of the recorded data, resulted in immediate repetition of investigation in this position.

Study Design and Statistical Methods

The study was designed as an open trial with a so-called split-plot design with the between-patients factor 'patient group' and the within-patients factor 'position'. Data analysis was performed by an independent statistician.

Variables of interest were described by means and standard deviations (SD). The variable power (μV²) was logarithmically transformed (base 10) to obtain an approximate normal distribution. For each of the three different frequency bands, the effects of patient group and position on log₁₀ power were assessed by using an ANOVA model. Multiple pairwise comparisons were adjusted according to the method of Tukey-Kramer. Measurements which correspond to outliers in ANOVA model residuals were identified and the analyses were repeated without them to assess their influence on results.

All reported p values are results of two-sided tests. A p value equal to or less than 0.05 was considered statistically significant. The SAS procedure GLM (SAS Institute, Cary, N.C., USA) was used to perform the ANOVA models. The SPSS statistical software package (SPSS, Chicago, Ill., USA) was used for all other calculations.

Results

In the very low frequencies, a significant influence of patient group (p = 0.035) and position (p = 0.032) on log₁₀ power was visible (fig. 1). Subsequent pairwise comparisons between different types showed that log₁₀ power was significantly lower in isolated axillary hyperhidrosis than in healthy controls (mean difference: 0.24, p = 0.020, 95% CI: 0.45, 0.03) (table 1). Comparing positions
Table 1: log_{10} power of all frequency bands for each type and position.

<table>
<thead>
<tr>
<th>Frequency band</th>
<th>Patient group</th>
<th>Mean of log_{10} power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>supine 1</td>
</tr>
<tr>
<td>Very low</td>
<td>axillary</td>
<td>2.18</td>
</tr>
<tr>
<td></td>
<td>palmoplantar</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>axillo-palmoplantar</td>
<td>2.37</td>
</tr>
<tr>
<td></td>
<td>healthy controls</td>
<td>2.43</td>
</tr>
<tr>
<td>Low</td>
<td>axillary</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>palmoplantar</td>
<td>2.37</td>
</tr>
<tr>
<td></td>
<td>axillo-palmoplantar</td>
<td>2.29</td>
</tr>
<tr>
<td></td>
<td>healthy controls</td>
<td>2.48</td>
</tr>
<tr>
<td>High</td>
<td>axillary</td>
<td>2.57</td>
</tr>
<tr>
<td></td>
<td>palmoplantar</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>axillo-palmoplantar</td>
<td>2.67</td>
</tr>
<tr>
<td></td>
<td>healthy controls</td>
<td>2.91</td>
</tr>
</tbody>
</table>

Pairwise revealed that log_{10} power was higher in supine 2 than in supine 1 (mean difference: 0.10, p = 0.026, 95% CI: 0.01, 0.19).

In the low frequencies, no influence of patient group (p = 0.25) on log_{10} power could be detected, but the effect of position was significant again (p = 0.0014) (fig. 2). Pairwise comparisons between different positions revealed that log_{10} power was significantly higher in the standing position than in both supine positions (table 1): mean difference to supine 1: 0.20, p = 0.0012, 95% CI: 0.07, 0.32; mean difference to supine 2: 0.14, p = 0.036, 95% CI: 0.01, 0.26.

In the high frequencies, the situation was more complicated, since a significant interaction between patient group and position was detected (p = 0.0077). As shown in table 1 and figure 3, in healthy subjects, the power in the high-frequency band decreases more at standing up than in patients with hyperhidrosis. Particularly in axillo-palmoplantar hyperhidrosis, the relative decrease of power at standing position compared to supine positions was less pronounced.

All analyses were repeated after exclusion of outliers detected by inspection of residuals. No remarkable differences compared to the results stated above were observed.

**Discussion**

Only few data exist on autonomic function in essential focal hyperhidrosis [1, 9–11]. Shih et al. [9] showed that patients with denervation of T2–3 ganglia because of palmar hyperhidrosis showed altered sweating response on
the whole body during physical exercise compared to normal subjects and patients suffering from palmar hyperhidrosis. Hyperhidrotic subjects with intact ganglia also showed less reflex bradycardia in response to the Valsalva manoeuvre, and a higher degree of cutaneous vasoconstriction in response to finger or cold immersion. The authors suggested an over-functioning of sympathetic fibres running through T2–3 as the cause of palmar hyperhidrosis, which leads to generalised autonomic dysfunction [9].

Other authors suggested that palmoplantar hyperhidrosis is only secondary to the hyperresponse to the mental or emotional stimulation of the sympathetic nervous system, and instead originates in the cerebral cortex [1].

Noppen et al. [11] reported a higher peak heart rate in subjects with focal hyperhidrosis at physical exercise, which normalises after sympatheticolysis. The authors concluded that sympathetic overactivity relevant to cardiac function in hyperhidrosis is only evident during sympathetic stimulation [11]. Nevertheless, most studies performed investigated primary palmar or palmoplantar hyperhidrosis, and no data are available on cardiac autonomic function in isolated axillary hyperhidrosis.

In our study, log10 power in the very-low-frequency band was significantly decreased in patients suffering from isolated axillary hyperhidrosis compared to healthy controls. Mechanisms and origins of very low frequencies are not sufficiently delineated yet [14]. However, short-term measurements of very low frequencies must be considered with great caution [13]. We used coarse-graining spectral analysis where non-harmonic elements are removed from the lower frequency bands, emphasising only the harmonic components [30].

Fleisher et al. [31] showed that power at very low frequencies increases when reducing the core temperature of normal subjects, but remains unchanged when skin temperature is increased or decreased, thus suggesting a specific thermoregulatory influence on this component related to core hypothermia. To our knowledge, no data on the change of very-low-frequency power at increase of core temperature exist. We speculate that the power of the very-low-frequency band might decrease under this condition, so an influence of central thermoregulation in axillary hyperhidrosis might be hypothesised. Nevertheless, our finding that power in very-low-frequency band hyperhidrosis is decreased in the axillary region when compared to normal subjects cannot be interpreted correctly as long as the mechanisms of very low frequencies are unclear.

The power of low frequencies is said to represent a complex combination of sympathetic and parasympathetic effects on cardiac autonomic function [14]. Although other authors have shown increased sympathetic activity in hyperhidrosis, leading to general autonomic failure [9] that is only evident at stimulation [11], no difference between hyperhidrotic and normal groups even at orthostatic stimulation was detected in our study. Although it has been suggested that sympathetic influence on low frequencies is rather indirect and they primarily reflect a parasympathetic mechanism [32], the lack of differences between groups in this frequency band was highly surprising.

High frequencies are mediated primarily by vagal innervation of the heart [14]. In our study, in hyperhidrotic subjects, the power of this frequency band decreased less at autonomic stimulation than in normal subjects. It was surprising to find a difference in this parasympathetically dominated frequency band. It has been reported that sympathetic dysfunction in primary focal hyperhidrosis is only visible during stimulation [11], but our data show that this might be true not only for the sympathetic, but also for the parasympathetic nervous system. This is a novel aspect, because dysfunction of the parasympathetic nervous system in focal hyperhidrosis has not been considered previously.
In summary, our findings are highly interesting: we found no evidence of sympathetic dysfunction as described in other patients who used different investigation techniques [9, 11]. Instead we observed parasympathetic dysfunction at autonomic stimulation in hyperhidrotic subjects compared to normal controls. Our results indicate that primary focal hyperhidrosis is based on much more complex dysfunctions of the autonomic nervous system than generalised sympathetic overactivity. Further studies should investigate this matter in detail.

References