Investigation of cutaneous microvascular activity and flare response in patients with fibromyalgia syndrome

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Abstract

Objectives. To assess microvascular activity in the skin of patients with fibromyalgia syndrome (FMS) as compared with normal controls.

Methods. Fifteen patients, who fulfilled the American College of Rheumatology criteria for FMS, and 15 age- and sex-matched healthy controls, were studied. The microvascular activity of the skin overlying the trapezius muscle was quantified using iontophoresis of acetylcholine as an endothelial-dependent vasodilator and sodium nitroprusside as an endothelial-independent vasodilator. We also studied the flare response by iontophoresing acetylcholine continuously for 10 min to stimulate a ring of nociceptor c-fibre endings in the skin.

Results. There was no significant difference in cutaneous vascular responses to short-duration iontophoresis of acetylcholine and sodium nitroprusside at the three different doses used. The area under the curve (AUC) (mean ± S.E.M.) for acetylcholine baseline, 20, 40, and 80 s were 6 ± 0.7, 23 ± 6, 45 ± 7 and 66 ± 10 AU for patients and 11 ± 4, 24 ± 3, 49 ± 7 and 62 ± 12 AU for controls, respectively (P = 0.2, 0.9, 0.7, 0.8, respectively). The corresponding figures for sodium nitroprusside were 5 ± 1, 18 ± 7, 51 ± 14 and 68 ± 14 AU for patients and 8 ± 3, 13 ± 2, 39 ± 5 and 61 ± 9 AU for controls, respectively (P = 0.2, 0.5, 0.4, 0.7, respectively). There was also no significant difference in the flare response in patients with FMS as compared with control subjects (119 ± 15 and 131 ± 13 AU, respectively; P = 0.57).

Conclusion. There are no significant differences in cutaneous microvascular reactivity between patients with FMS and control subjects.

KEY WORDS: Flare response, Microvascular function, Fibromyalgia syndrome.

Fibromyalgia syndrome (FMS) is a poorly understood complex syndrome characterized by pain amplification, musculoskeletal discomfort and systemic symptoms. Patients have well-defined reproducible myofascial tender points. The syndrome can be either primary or secondary to an underlying condition. The diagnostic criteria produced by Wolfe et al. [1] are valid for both primary and secondary FMS. It is associated with non-restorative sleep pattern with abnormalities of stage IV non-rapid eye movement sleep. The prevalence of FMS in the general population is 2% (3.4% in women and 0.5% in men) [2]. This increases with age, with the highest values attained between 60 and 70 yr (>7% in women). However, the prevalence has been estimated to be 5% in a general in-patient population [3], and it is the third or fourth most common reason for rheumatological referral [4]. It is a chronic condition and the level of pain and functional disability with respect to activity of daily living are similar to those found in patients with rheumatoid arthritis [5]. Treatment is often ineffective and outcome is poor [6, 7].

Research into possible abnormalities in muscle structure and function has been largely unrewarding [8]. Most investigators believe that the muscle abnormalities are secondary to inactivity and pain. However, these abnormalities may reflect a generalized change in the peripheral nervous system [9] and/or skin and muscle blood flow [8].

It has been suggested that increased cutaneous nociception is part of a possible pathophysiological model in FMS [8]. The presence of tender points, including the skin fold overlying the upper part of the trapezius in patients with FMS, implies that these patients may have a hyperalgesic syndrome. Alteration in the function of c-fibre nociception may explain the hyperalgesia in patients with FMS [10]. The local functions, such as vasodilatation and axon reflex flare reaction, are
mediated via local release of different substances. In animal studies, the polymodal nociceptor afferents have been shown to be the main contributor to axon reflex flare and other neurogenic inflammatory responses involving vasodilatation [11]. A technique for quantifying the flare response as a function of c-fibres has been described [12, 13]. Accordingly, we designed our study with the aim of assessing microvascular reactivity and flare response as a function of nociceptron c-fibres and to determine whether any of these are involved in the symptoms and signs in FMS patients.

Patients and methods

Tayside Committee on Research Medical Ethics approved the study. All subjects were given a written information sheet and written informed consent was obtained. Fifteen patients who fulfilled the American College of Rheumatology criteria for FMS [1] and were recruited from the rheumatology out-patient clinic and 15 age- and sex-matched healthy controls were studied. The control subjects were selected healthy subjects from the department and friends of the patients. The controls were assessed carefully by history and examination to ensure they did not have FMS. Subjects with no myalgic pain, significant sleep disturbance or fibromyalgia trigger points were recruited as controls. Subject details including age, sex, smoking habit, disease duration and current drug treatment were all recorded. Patients taking tricyclic antidepressants for their FMS were asked to discontinue them 4 weeks before the assessment. The severity of fibromyalgic symptoms was assessed using the following parameters:

(a) Visual Analogue Scale (VAS) consisting of a 10 cm line on which patients recorded the degree of pain experienced in the preceding week;
(b) number and site of tender spots based on the 18 points identified by Wolfe et al. [1];
(c) Stanford Health Assessment Questionnaire (HAQ) as modified by Kirwan and Reeback [14];
(d) Hospital Anxiety and Depression questionnaire (HAD) [15];
(e) number of nights in the last week in which difficulty with sleep was experienced;
(f) average number of hours slept each night over the previous week;
(g) resting pulse and blood pressure.

Assessment of cutaneous vascular reactivity and flare response

Following at least a 2-h fast with no smoking during this period, the subjects were seated in a constant temperature room at 21°C. The subjects were seated and acclimatized to the above conditions for 30 min.

Blood flow (termed skin erythrocyte flux) was measured continuously using single-point laser Doppler flowmetry with the laser probe positioned at the centre of the iontophoretic electrode (Fig. 1A). We used the MIC1 iontophoresis controller, which was directly controlled by an output from the MBF3D Laser Doppler Perfusion Monitor (Moor Instruments, Axminster, UK). All iontophoresis data were transferred to an IBM personal computer using dedicated software for data analysis.

The vascular responses were measured on the skin overlying the upper part of the trapezius. Assessments of endothelium-dependent and endothelium-independent vascular responses were made during short-duration iontophoresis of acetylcholine and sodium nitroprusside, respectively. Acetylcholine and sodium nitroprusside were iontophoresed for 20 s using 0.1 mA anodal and cathodal currents, respectively, giving a total charge of 2 millicoulombs (mC). To increase the dose, both substances were also iontophoresed for 40 and 80 s (i.e. 4 and 8 mC). Vascular responses were measured directly over the iontophoresis site for 4 min after each dose.

The flare response was quantified by iontophoresing acetylcholine to stimulate a ring of nociceptive c-fibre endings at the centre of which the increase in blood flow was measured with a laser Doppler flowmeter [12, 13, 16]. A plastic iontophoretic electrode (8 mm in height, outer diameter 30 mm, inner diameter 8.5 mm, Fig. 1B) was attached by a double-sided adhesive disc to the skin overlying the upper part of the trapezius avoiding underlying veins. After the 30 min of stabilization, baseline measurements of blood flow were made. The outer well of the capsule was filled with 1% acetylcholine, which was iontophoresed into the skin continuously for 10 min.

Statistical analysis

For blood flow measurements the area under the curve (AUC) was calculated. The response was expressed as the difference between the AUC after iontophoresis and the basal AUC. The differences in microvascular and flare responses between FMS patients and control subjects were tested using the unpaired t-test. For dose–response curves, differences in the AUC between FMS patients and control subjects were tested using two-way analysis of variance for repeated measures. We used the unpaired t-test for normally distributed data and the Wilcoxon signed rank test for data that were not normally distributed to assess differences between the groups. A P value of < 0.05 was considered as statistically significant.

Results

Details of the patients and controls are shown in Table 1. Thirteen FMS patients had 18 out of 18 fibromyalgia tender points, one had 16 and another had 17. The patients were in significant pain at the time of the study (average VAS for pain 6.66 out of 10).

Five subjects from the control group had some positive tender fibromyalgia points (one had one, one had two, one had three, one had four and one had seven tender points). One control subject had been excluded.
as she fulfilled the diagnostic criteria for FMS. She had 18 tender points, VAS for pain of 9, HAD anxiety of 8 and HAD depression of 5, slept badly 7 days a week, average sleep was 7 h, but her HAQ score was 0.

Patients with FMS had significantly higher HAQ ($P < 0.0001$) and anxiety and depression HAD scores ($P < 0.0027$ and $0.0002$, respectively), indicating higher functional disability, and anxiety and depression compared with the normal control subjects. They also had a significantly greater number of disturbed nights ($P < 0.013$).

Two-way analysis of variance showed no significant differences in cutaneous vascular responses to acetylcholine and sodium nitroprusside at the three doses used. AUC (mean ± s.e.m.) for acetylcholine baseline, 20, 40, and 80 s were $6 ± 0.7$, $23 ± 6$, $45 ± 7$ and $66 ± 10$ AU for patients and $11 ± 4$, $24 ± 3$, $49 ± 7$ and $62 ± 12$ AU for controls, respectively ($P = 0.2$, 0.9, 0.7, 0.8, respectively). The corresponding figures for sodium nitroprusside were $5 ± 1$, $18 ± 7$, $51 ± 14$ and $68 ± 14$ AU for patients and $8 ± 3$, $13 ± 2$, $39 ± 5$ and $61 ± 9$ AU for controls, respectively ($P = 0.2$, 0.5, 0.4, 0.7, respectively) (Figs 2, 3). Although blood pressure was significantly higher in patients with FMS, there was no significant correlation between skin erythrocyte flux and blood pressure.

Furthermore, there was no significant difference in the flare response to iontophoresis of acetylcholine.
for 10 min in patients with FMS and control subjects (values are means ± S.E.M.).

Discussion

As had been found in previous studies [10, 17, 18], our FMS patients had significant functional disability, pain, anxiety and depression, which need to be considered in managing these patients. They also had significantly higher blood pressure, which is possibly related to their distress. When compared with the control group, there was no difference in the average number of hours slept during the night, but they had significantly more disturbed sleep.

In contrast to our study, Jeschonnek et al. [19], found significant differences in the vascular assessment between patients with FMS and healthy controls. However, this study measured only baseline vascular activity without the full assessment of endothelial-dependent and -independent stimulation, as in our study. Accordingly, our study did not support the theory which suggests that possible abnormalities in skin blood flow may explain some of the FMS, as suggested by Goldenberg [8].

Schmelz et al. [20] found that the flare response in human skin depends on the excitation of mechano-insensitive C-fibres. They found that to stimulate these fibres a stimulus above 25 mA is needed. However, in our study we used a different technique to induce the flare response, by iontophoresing acetylcholine and using the electrical current for that purpose but not for stimulation. This method of inducing the flare response has been used for the quantitative assessment of peripheral nociceptive c-fibre function in several studies [12, 13, 16]. It has also been shown that an impaired flare response (using a similar iontophoresing protocol) in patients with diabetes and neuropathic foot lesions correlates with the clinical diminution of pain sensation [16]. It would be of interest in the future to determine if the method of Schmelz et al. produces a similar result in FMS patients.

Although it has been suggested that increased cutaneous nociception is part of a possible pathophysiological model in FMS [8], our study demonstrated that there was no significant abnormality in the flare response in the skin overlying the trapezius in FMS patients as compared with healthy controls. Thus, it is unlikely that an increased nociception is the result of increased c-fibre function.

Labossy et al. [21] found that patients with FMS have significantly more cold-induced vasospasm compared with healthy controls, indicating some abnormalities in vasoconstriction. However, in our study we found that there is normal endothelial function and nitric oxide activity. However, abnormal levels of vasoconstrictors produced by the endothelium remain a possibility. It has been suggested that abnormalities in the autonomic nervous system may play an important role in the pathogenesis of FMS [22, 23]. An abnormal autonomic nervous system may explain the multisystem symptoms of FMS including the disturbed sleep, fatigue, sicca symptoms, increased skin hyper-reactivity and cold sensitivity and the Raynaud’s-like phenomenon, as well as irritable bowel syndrome. However, as we have not shown any abnormalities in either the flare or the

Fig. 2. Skin vascular response to short-duration iontophoresis of acetylcholine in 15 patients with FMS and 15 control subjects (values are means ± S.E.M.).

Fig. 3. Skin vascular response to short-duration iontophoresis of sodium nitroprusside in 15 patients with FMS and 15 control subjects (values are means ± S.E.M.).

Fig. 4. Skin flare response to iontophoresis of acetylcholine for 10 min in 15 patients with FMS and 15 control subjects (values are means ± S.E.M.).
vascular responses, autonomic nervous system dys-
function is unlikely, as the autonomic nervous system
is dependent on unmyelinated peripheral fibres to
produce blood flow changes.

Other investigators have found abnormalities in
regional cerebral blood flow and generalized low pain
threshold, suggesting that the abnormal pain percep-
tion in FMS patients may result from a functional
abnormality within the central nervous system [24].

Conclusions

There are no significant differences in nociceptor c-fibre
function activity, as measured by skin blood flow
techniques, between patients with FMS and controls.
Cutaneous microvascular reactivity in the skin overlying
the trapezius is not altered in FMS patients.

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