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Muscle Tissue Oxygen Pressure in Primary Fibromyalgia

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Trigger points in painful muscle are a characteristic sign in patients with primary fibromyalgia. The MDO oxygen electrode was used to evaluate oxygenation in the subcutaneous tissue and in trigger points in the trapezius and brachioradial muscles. Ten patients and 8 normal controls were studied. The results in the patients were abnormal, with scattered or slalom-slope histograms, indicating low tissue oxygenation. The controls were normal, except in one case. The conclusion is that in patients with primary fibromyalgia, the muscle oxygenation is abnormal or low, at least in the trigger point area of the muscles.

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Primary fibromyalgia (PF) is a non-articular rheumatic disease, also known as 'fibrositis', 'myofascial syndrome' and 'muscle rheumatism'. It is predominantly a female disease characterized by chronic pain and stiffness in skeletal muscles and joints, but without arthritic manifestations. A typical feature is the painful trigger-points in muscles and tendon insertions (29).

In 1973 Fassbender & Wegner published a morphologic study on the pathogenesis of PF (3). Biopsies from the trapezius muscle were studied with light- and electronmicroscopy. Among their findings were swollen endothelial cells of the muscle capillaries. They hypothesized that local hypoxia was a possible cause of the development and symptoms of the disease. However, there is, no published investigation which has actually proved the existence of muscle hypoxia in PF.

In 1966 Lübbers & Kessler described a multipoint oxygen electrode (the MDO electrode, Mehrdraht Dortmund Oberfläche) for measuring oxygen pressure fields on organ surfaces (6). This MDO oxygen electrode has been used extensively in physiological research (15, 20, 23). Since the development of a disinfection technique (16), the MDO electrode has also been used in human studies (17, 18, 24). A complete system for computerized on-line measurements of tissue surface oxygen pressures was later described (30).

The purpose of the present study was to elucidate whether or not muscle hypoxia exists in PF-patients, and to compare the findings in these patients with the results from a group of healthy volunteers.

MATERIAL AND METHODS

Ten patients and 8 healthy volunteers were studied. All patients fulfilled the diagnostic criteria of Yunus et al. (Table I) (29). In the patient group, 9 were female and 1 male, with a mean age of 43 years (range 22–58). On average the patients had had symptoms of PF for 3 years (range 2–10). There were no symptoms or signs of any other rheumatological or neuromuscular disease that could explain the symptoms of the patients and no patient had clinical hypoxia (for example from chronic obstructive lung disease). Arterial blood samples for gas analysis were not taken. The volunteer group consisted of healthy females only, with a mean age of 36 years (range 26–43).

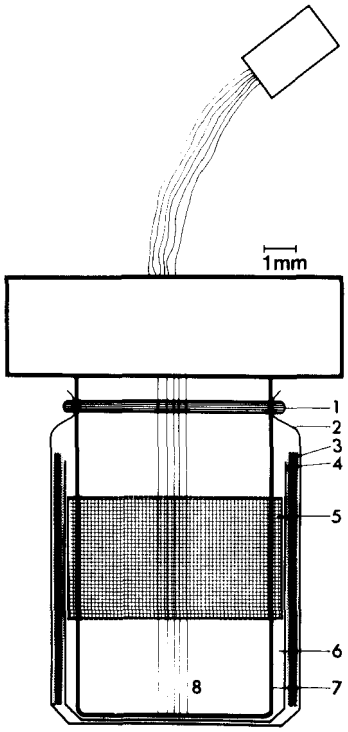

Fig. 1. The MDO oxygen electrode. *1*, Rubber ring to hold the Teflon membrane. *2*, Teflon membrane. *3*, Lucite ring to hold the cellophane membrane. *4*, Cellophane membrane. *5*, Ag/AgCl-anode. *6*, Electrolyte solution (0.2 M KCl). *7*, Glass nucleus. *8*, Eight platinum wires. Reproduced with kind permission of Acta Anaesth Scand.

Routine laboratory tests including erythrocyte sedimentation rate, hematology count, electrolytes, creatinine, creatine phosphokinase, thyroid function, rheumatoid factor and antinuclear antibody were normal in all patients.

A trigger point was defined as a localized area of intense pain on compression of the muscle, often with radiation of pain, and often so painful that the patient jumped on palpation. Trigger points are often found in the trapezius muscle, which was therefore the initial choice for oxygen measurements (29). Later in the study both the trapezius and the brachioradial muscles were studied. The reasons for this were our initial findings in the trapezius muscle and the fact that the only normal material

Table I. *Diagnostic criteria of primary fibromyalgia (Yunus, 1981)*[a]

1. Obligatory criteria:
(*a*) Presence of generalized aches and pains or prominent stiffness, involving at least three anatomic sites for at least 3 months.
(*b*) Absence of secondary causes, e.g. traumatic, other rheumatologic, infective, endocrine or malignant.

2. Major criteria:
Presence of at least 5 typical and consistent tender points.

3. Minor criteria:
(*a*) modulation of symptoms by physical activity; (*b*) modulation of symptoms by weather factors; (*c*) aggravations of symptoms by anxiety or stress; (*d*) poor sleep; (*e*) general fatigue or tiredness; (*f*) anxiety; (*g*) chronic headache; (*h*) irritable bowel syndrome; (*i*) subjective swelling; (*j*) numbness.

[a] PF-patients must satisfy the two obligatory criteria, by definition, as well as the major criterion plus at least three minor criteria. If the patient has only 3 or 4 tender points, five minor criteria are suggested.

available for comparison was a group studied in 1980 by Lund and co-workers, who used the brachioradial muscle (17).

Measurements of tissue surface oxygen pressure fields were performed with the MDO oxygen electrode (Fig. 1) (6, 20, 30). This electrode is constructed according to the Clark principle and has eight separate and individually registering measurement points (1). Under surgically aseptic conditions and under subcutaneous local anesthesia (10 ml 0.25% bupivacaine per measurement site) an incision was made through the skin over a trigger point located in the trapezius and the brachioradialis muscles, respectively. Tissue pO_2 (p_tO_2) was also measured in the subcutaneous tissue in some of the subjects. Thus, a disinfected oxygen electrode was initially placed on the subcutaneous tissue for measurements (for a full description of methodology and equipment, see Lund, 1979) (16, 14). After the subcutaneous measurements, the fascia was opened and the muscle surface was freed with the utmost care to avoid trauma to the muscle surface (12, 15).

To obtain a sufficient number of observations ($n>80$) for statistical evaluation and to enable construction of the tissue oxygen pressure field histograms, eight oxygen pressure values (one from each measuring point) were collected every 15 sec (20). Usually 120 single oxygen pressures were collected for a histogram, i.e. the total sampling time for one histogram was 210 sec. The oxygen pressure values were then fed into an ABC 800 computer (Luxor AB, Motala, Sweden) and corrected for electrode drift, local tissue temperature and air pressure. Histograms were obtained during spontaneous breathing of ambient air.

A normal histogram is Gaussian in shape with a mean usually between 1.3 kPa (10 mmHg) and 4.7 kPa (35 mmHg) when measured on skeletal muscle (9, 17, 20). Abnormal histograms are of two types: one looks like a slalom slope and usually begins at the origin. In the other the registered values are widely scattered, though a scattered histogram may have the same mean p_tO_2-value as a normal histogram. The slalom slope type indicates impaired tissue oxygenation, whereas the exact meaning of the scattered type is still under discussion (18, 20).

Statistical methods

Comparisons between pO_2 group means were made using paired t-test (13). A parametric test, e.g. Student's t-test, can be applied to oxygen pressure histograms only when all histograms included are of the normal type. Statistically significant differences were determined at the levels indicated in text. All mean values are given ± standard deviation (SD).

A histogram is described by its mean, standard deviation, skewness, kurtosis and distribution type. A statistical method for testing one histogram against another must be independent of the mean values, as the mean does not necessarily change from one measuring situation to another, even though a definite biological change may have taken place (20). Changes in distribution types were tested with the non-parametric two-sample Kolmogorov-Smirnov test (13) as modified by Ödman & Lund (30), which provides an analysis independent of the mean and enables one to calculate the significance level at which the hypothesis of equal distributions can be rejected.

RESULTS

Measurements in the subcutaneous (fat) tissue superficial to the trapezius muscle were made in 7 patients and 6 control subjects. The results are given in Table II. One patient histogram and one control histogram are shown in Fig. 2. The total mean tissue pO_2 in the patients (6.0 kPa = 45 mmHg) was significantly lower than that in the controls (8.7 kPa = 65 mmHg), with $p<0.01$. Most of the histograms in this tissue were of the normal type, with only one clearly abnormal histogram among the patients.

The trapezius muscle oxygen pressure results are given in Table III. Scattered histograms, one example shown in Fig. 3, were obtained in all patients except one who had a slalom slope histogram. In the control group, standard deviations were small and all histograms were normally bell-shaped; one example is shown in Fig. 3.

Brachioradial muscle oxygen pressures were measured in 4 patients and 5 controls; the results are presented in Table IV. A typical histogram is shown in Fig. 4. The findings in this muscle paralleled those in the trapezius, i.e. in the patient group 3 out of 4 histograms were abnormal, while in the control group only 1 of 5 was abnormal. One histogram in the patient group was of an intermediate type close to normal, and one histogram in the control group was frankly scattered.

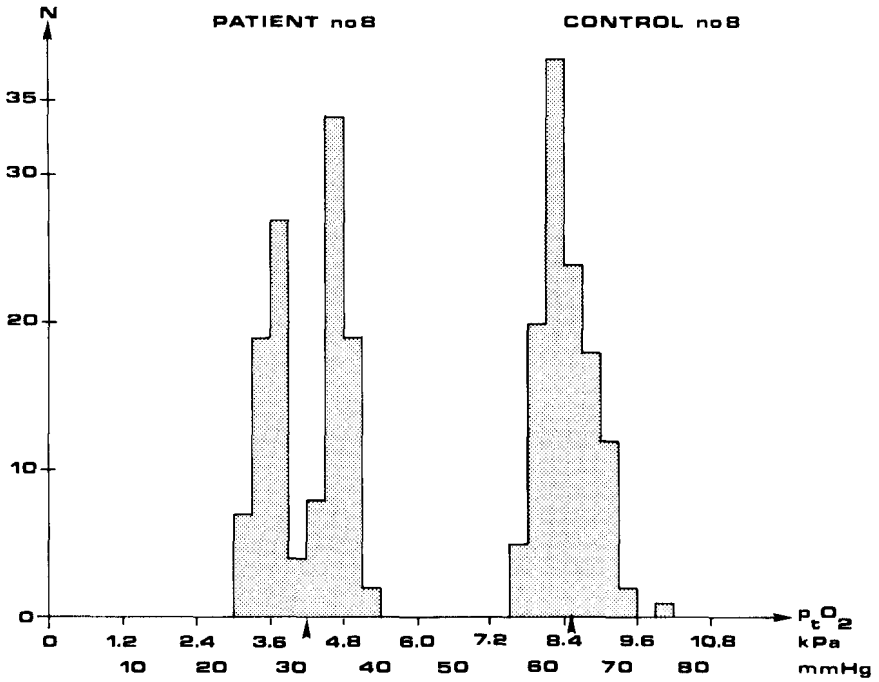

Fig. 2. Histograms registered in the subcutaneous tissue. The histogram from the control is normal, the histogram from the patient begins to scatter. Abbreviations: *N*, number of observations; p_tO_2, tissue oxygen pressure. The arrow at the abscissa indicates the mean tissue oxygen pressure.

Table II. *Subcutaneous tissue oxygen pressure in kPa*

Subjects	Case no.	p_tO_2[a]	SD	S	K	HDT
PF patients	1	4.3 (32)[b]	0.36	0.17	−1.12	N
	3	8.5 (64)	0.62	−0.04	−1.38	N
	5	8.9 (67)	0.25	−0.04	−0.56	N
	6	6.1 (46)	0.37	−0.59	−0.09	N
	7	5.5 (41)	0.99	−0.26	−1.29	Sc
	8	4.2 (31)	0.56	−0.14	−1.47	N/Sc
	9	4.6 (35)	0.48	−0.57	−1.26	N
Mean		6.0 (45)	1.97			
Controls	1	8.3 (62)	0.32	0.03	−0.50	N
	2	7.7 (58)	0.85	0.38	−0.54	N
	4	9.5 (71)	0.80	−0.22	−1.41	N/Sc
	5	9.8 (74)	0.39	−0.02	−0.56	N
	7	8.8 (66)	0.52	−0.09	−0.90	N
	8	8.5 (64)	0.42	0.69	0.43	N
Mean		8.7 (65)	0.78			

[a] Abbreviations: p_tO_2, mean tissue oxygen pressure; SD, standard deviation; S, skewness; K, kurtosis; HDT, histogram distribution type (N = normal, L = low ski-slope, Sc = scattered). – [b] Values in parentheses are mmHg.

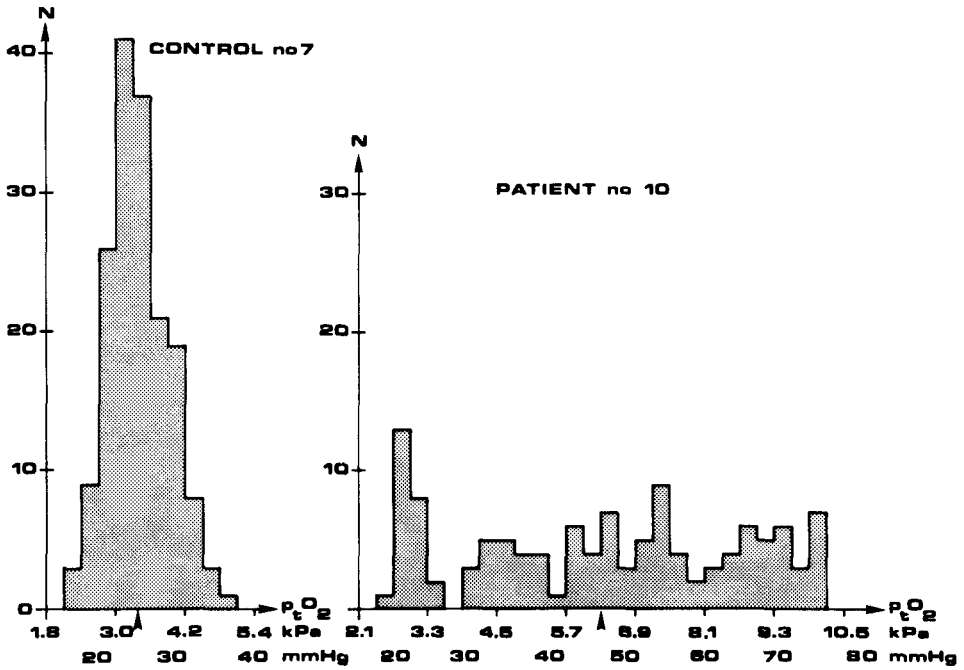

Fig. 3. Histograms registered in the trapezius muscle. The histogram distribution types are statistically different, with $p<0.001$. Abbreviations: see Fig. 2.

Table III. *Trapezius muscle oxygen pressure in kPa*

Abbreviations: see Table II. Values in parentheses are mmHg. The total mean is not given, since the PF-patients and the controls have different HDT. See further under Methods

Subjects	Case no.	P_tO_2	SD	S	K	HDT
PF patients	1	5.9 (44)	0.89	0.07	−0.61	Sc
	2	1.4 (11)	0.37	−0.57	−0.45	L
	3	1.5 (11)	1.29	0.75	−0.66	Sc
	4	3.8 (29)	1.04	0.16	−1.20	Sc
	5	7.2 (54)	2.25	0.84	−0.72	Sc
	6	3.7 (28)	1.23	−0.97	0.55	Sc
	7	2.3 (17)	0.95	−0.65	−0.67	L/Sc
	8	2.0 (15)	1.80	0.57	−1.54	Sc
	9	5.5 (41)	1.62	1.03	−0.20	Sc
	10	6.3 (47)	2.34	−0.05	−1.24	Sc
Controls	1	7.1 (53)	0.65	−0.02	−0.48	N
	2	3.0 (23)	0.91	0.71	0.46	N
	3	5.5 (41)	0.69	−0.34	0.03	N
	4	5.3 (40)	0.56	−0.29	−0.54	N
	5	9.4 (71)	0.78	0.84	0.76	N
	6	3.2 (24)	0.53	−0.10	0.64	N
	7	3.4 (26)	0.53	0.34	−0.16	N
	8	6.7 (50)	0.41	−0.76	1.09	N

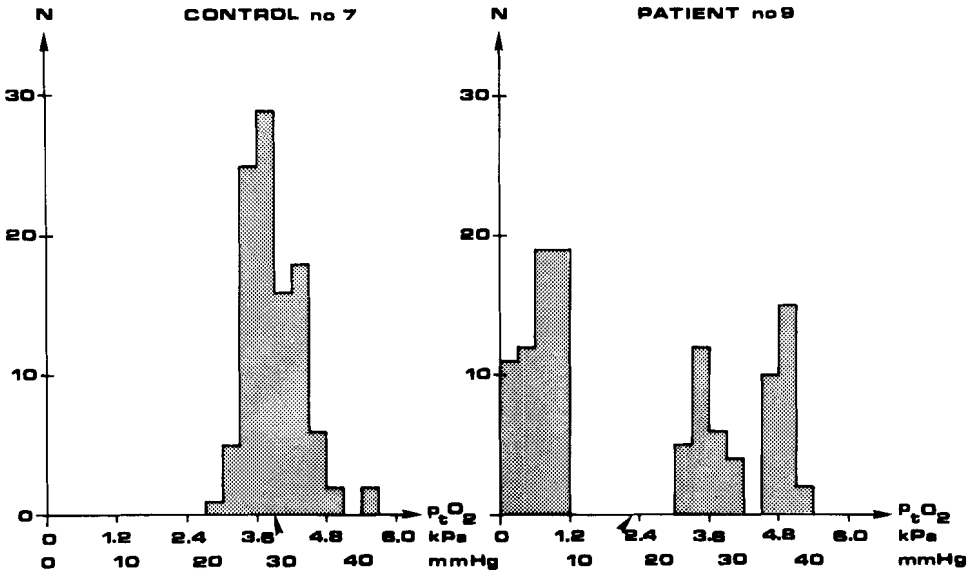

Fig. 4. Histograms registered in the brachioradial muscle. The histogram distribution types are statistically different, with $p<0.001$. Abbreviations: see Fig. 2.

Statistical testing of the subcutaneous tissue histogram distribution types showed no differences between patients and the control group. However, testing of histogram distribution types in the trapezius and the brachioradial muscles, respectively, showed statistical significance ranging from $p<0.05$ to $p<0.001$.

DISCUSSION

Several factors are thought to interact to produce the PF-syndrome, e.g. overload, disturbed sleep and psychogenic factors, all possibly causing muscle tension or spasm (27).

Table IV. *Brachioradial muscle oxygen pressure in kPa*

Abbreviations: see Table II. Values in parentheses are mmHg. The total mean is not given, since the PF-patients and the controls have different HDT. See further under Methods

Subjects	Case no.	P_tO_2	SD	S	K	HDT
PF patients	7	3.7 (28)	0.87	0.76	−0.93	Sc/N
	8	6.9 (52)	1.16	−0.22	−0.68	Sc
	9	2.3 (17)	1.82	0.25	−1.67	Sc
	10	8.7 (66)	0.90	−0.05	−1.29	Sc
Controls	4	6.3 (47)	0.56	0.33	2.06	N
	5	10.5 (79)	0.53	0.21	−0.63	N
	6	3.7 (28)	1.13	−0.28	−1.41	Sc
	7	3.9 (29)	0.49	0.82	1.23	N
	8	2.7 (20)	0.64	−0.20	−0.65	N

In addition to these factors, Fassbender & Wegner hypothesized that hypoxia was an essential and causative factor in the PF-syndrome (3).

With the development of the MDO-electrode it has become possible to measure tissue oxygen pressures with a high degree of accuracy (6, 14, 20). Studies performed with needle-type electrodes had drawbacks: the needle compressed the tissue, the relation of the needle to the vascular bed was unknown (19, 25, 28). In order to avoid these drawbacks, Lübbers & Kessler developed an electrode (MDO) with eight individually registering points, to be used on tissue surface (6, 8). This technique is non-traumatic to the tissue and the weight of the electrode so light that pressure ischemia is not induced (7, 30). Measuring at 8 points simultaneously avoids the problem of the relationship of the electrode to the vascular bed (20). Tissue oxygenation is constantly varying with changes in local capillary blood flow, hemoglobin oxygen affinity and metabolism (4, 21, 23). The sum of these variations is thus registered with the electrode, and in order to describe the dynamically varying oxygen pressure field, at least 80 individual oxygen pressures must be registered (14, 20). The catchment zone of each measuring point is hemispherical and reaches approximately 20 μm into the tissue (24). Studies initially performed in different animals (8, 15, 26) and later in humans (2, 5, 14, 17, 24) have led to the recognition of three basic types of oxygen pressure histogram; the normal Gaussian-shaped type, and 2 abnormal types. One consists of only low values (the slalom slope type) close to the origin, clearly indicating tissue hypoxia. The other type shows a scattering of oxygen values along the *x*-axis (Fig. 3). The meaning of a scattered histogram has, as yet, not been finally defined, though maldistribution of capillary blood flow has been hypothesized. However, neither the slalom slope type nor scattered histograms have been found in any normal situation (2, 5, 9, 15, 17, 18, 20, 23, 24). In hypoxemia or hyperoxemia, histograms either change immediately to the slalom slope type or first to the scattered type and then to the slalom slope type (2, 5, 17, 18).

To minimize trauma to the patient, no arterial blood samples were taken for blood gas analysis, though no signs of clinical hypoxemia (cyanosis, dyspnea, tachycardia, etc.) were seen. Had the subjects been hypoxic (or even hyperoxic, e.g. through an increase of the inspired oxygen fraction), this would have led to either type of abnormal histogram.

Local anesthetics are myotoxic agents. Great care was therefore taken to inject the anesthetic only into the superficial subcutaneous tissue. That bupivacaine injected in this way does not influence microcirculatory flow in the underlying muscle has previously been shown (15). Thus the local anesthetic should not have affected the muscle measurements. Whether it had any effect on the subcutaneous measurements is impossible to ascertain, though in the present study the findings showed a consistently normal pattern. Thus, addition of the histograms and testing of mean values with the *t*-test was permitted. The histograms obtained in the patient group were centered around lower mean values, so much so that the two groups were differed statistically with $p<0.01$. Subcutaneous tissue pO_2 has never before been studied with the MDO-electrode, but studies with implanted Silastic catheters and subcutaneous gas pockets have shown oxygen pressures at the same level as those obtained in the controls in this study (11, 22). The results from the trapezius muscle and the brachioradial muscle parallel one another in that we almost exclusively found abnormal histograms in the patients and normal in the controls.

Oxygen pressure fields in the trapezius muscle have never been studied before. However, there are a few published studies on humans utilizing the brachioradial muscle (17, 18). A comparison of the results of the measurements in the brachioradial muscle in the controls of the present study, versus those obtained by Lund et al. in healthy volunteers revealed no statistically significant differences (17). Furthermore, the results from the trapezius muscle measurements in the control group in this study did not differ from either

the brachioradial controls or the earlier brachioradial group studied by Lund et al. (17). Thus the findings in the trapezius and the brachioradial muscles of the PF-patients indicate an abnormal oxygenation, possibly due to morphological or functional changes affecting the microvessels in the trigger points. The significantly lower total mean oxygen pressure in the subcutaneous tissue of the patients, although not hypoxic, might indicate that PF also affects tissues other than skeletal muscle.

Among other factors, the tissue oxygen pressure depends on capillary blood flow and metabolism (4, 21). Blood flow in fibromyotic muscles was studied by Klemp et al. (10). They injected ^{133}Xenon, 0.1 ml, into trigger points in the trapezius muscle. They found no significant changes in local blood flow in the fibromyotic group compared with a normal group. However, the results from the ^{133}Xenon-clearance technique and the MDO electrode cannot be compared. Lund et al. also tried to relate the capillary flow changes (measured with ^{133}Xenon and ^{51}Cr-EDTA) induced by changes in arterial pO_2 to changes in tissue oxygen pressure fields (17, 18). No correlations were found, since the MDO-electrode measurement volume is extremely small, and even the small volume of tracers used (0.03 ml) was approximately 10^6 times greater than the electrode catchment volume (17). Thus, tissue pO_2 measurements have a much higher power of resolution than ^{133}Xenon-clearance and therefore these two methods need not correlate. Furthermore, with the greater tissue volume measured with the ^{133}Xenon technique, local maldistribution of flow may remain undetected, whereas it can be seen in the abnormal oxygen histograms.

To conclude, we have found evidence of abnormal tissue oxygenation in muscle with trigger points in patients with PF as measured with the MDO oxygen electrode. Studies employing modern techniques elucidating the tissue metabolic state of the trigger points may confirm these findings.

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