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Autonomic neuropathy and transcutaneous oxymetry in diabetic lower extremities

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Summary Transcutaneous oxygen tension is a useful method with which to assess the functional status of skin blood flow. The reduced values observed in diabetic patients have been interpreted as a consequence of peripheral vascular disease. However, diabetic patients show lower transcutaneous oxygen tension values than control subjects with equivalent degrees of peripheral vascular disease, suggesting that additional factors are involved. Since the autonomic nervous system influences peripheral circulation, we studied the relationship between autonomic neuropathy and foot transcutaneous oxymetry in non-insulin-dependent diabetic (NIDDM) patients without peripheral vascular disease. The following age-matched patients were selected and evaluated: control subjects, C, ($n = 20$), NIDDM patients without autonomic neuropathy, D, ($n = 16$) and with autonomic neuropathy, DN, ($n = 20$). All diabetic patients showed lower transcutaneous oxygen tension values than control subjects, while no differences were observed between the diabetic patients with and without autonomic neuropathy. In addition the saturation index that increases in the presence of autonomic neuropathy does not correlate with foot TcPO_2. In conclusion autonomic neuropathy does not influence foot TcPO_2 and therefore it is unlikely that it contributes to development of foot lesions during induction of foot skin ischaemia. [Diabetologia (1994) 37: 1051–1055]

Key words Diabetic autonomic neuropathy, transcutaneous oxymetry, galvanic skin response, blood oxygen content, diabetic foot.

There is evidence to show that diabetes mellitus causes a reduction in limb TcPO_2 [1, 2]. TcPO_2 is directly related to skin oxygen delivery and the degree of hypoxia has been correlated with clinical symptoms of peripheral ischaemia [3]. However, diabetes causes a reduction in limb TcPO_2 beyond that which can be accounted for by large-vessel occlusive arterial disease alone [4].

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Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus; TcPO_2, transcutaneous oxymetry; A-V, arterio-venous shunts; PVD, peripheral vascular disease; HbA_{1c}, glycated haemoglobin; SI, saturation index.

The autonomic nervous system plays an important role in regulating peripheral blood flow with sympathetic nerve fibers regulating flow through their action on the A-V shunts physiologically dedicated to thermal regulation [5]. The failure of sympathetic control results in a vasodilatation with increased flow through the A-V shunts and therefore an increased total peripheral blood flow [6]. This could be associated with a reduced flow in nutritional capillaries (capillary steal) and explain the coexistence of increased peripheral skin blood flow and of cutaneous ulceration in patients with autonomic neuropathy [7]. According to this line of reasoning the low TcPO_2 values observed in diabetic patients might be the consequence of peripheral autonomic neuropathy. Therefore, our aim was to evaluate the influence of peripheral autonomic neuropathy on TcPO_2.

Patients and methods

Patients. This study was approved by the Ethical Committee of the University of Rome "Tor Vergata" and informed consent was obtained from all subjects. After a thorough interview to eliminate any potential interfering neurological condition (alcohol addiction, thyroid disease, lumbar root disease, etc.) 56 subjects were enrolled in the study. In order to exclude significant peripheral vascular disease or major vascular complications, the patients were evaluated by Doppler ultrasound technique and only those showing an ankle/brachial index between 0.9 and 1.1 were included in the study.

All the patients were non-smokers, normotensive and none were taking drugs affecting blood pressure. The subjects were distributed into three groups: group C: 20 control subjects; group D: 16 NIDDM patients without autonomic neuropathy; group DN: 20 NIDDM patients with autonomic neuropathy. Diabetic patients were included in the group with neuropathy in the presence of at least two abnormal cardiovascular tests for autonomic function and absent galvanic skin response (see below), and in the group without neuropathy in the presence of normal values for all cardiovascular tests and present galvanic skin response. This test was chosen because it has been already used to investigate the function of small unmyelinated sympathetic fibers in the limbs of diabetic subjects [8, 9]. Clinical characteristics of the subjects are given in Table 1. The following tests were applied to all the subjects:

1] Transcutaneous oxymetry ($TcPO_2$): $TcPO_2$ (Kontron, Roche inc., Everett, Mass., USA) values were recorded for 1 h and a half on the chest and on the dorsum of each foot, with the patient resting in the supine position. Recordings were made at an electrode temperature of 44.1 °C [10]. Room temperature was maintained between 24–26 °C.

2] Arterial and venous partial pressure of oxygen (PaO_2, PvO_2) and oxygen content: determined by the autoanalyzer radiometer (ABL 330 with OSM 3 Hemoximeter Copenhagen, Denmark). Arterial blood was drawn from the radial artery and venous blood from a superficial vein on the dorsum of each foot. The percentage of oxygen saturation in the peripheral veins was calculated by applying the following formula: saturation index (SI) = PvO_2/PaO_2% [11].

3] Cardiovascular autonomic function: assessed by four cardiovascular tests: heart rate variation on deep breathing, on lying to standing and during the Valsalva manoeuver, blood pressure fall on standing. Tests were always performed in the morning and evaluated according to standard procedures [12].

4] Galvanic skin response (GSR): GSR measurements were recorded from the sole of the foot, after a sensory stimulus was applied to the controlateral foot. The patients with a clear biphasic response were classified as GSR present, the patients without any response were classified as GSR absent, all others being excluded [13].

5] Vibratory perception threshold(VPT): vibratory sensitivity was measured with a Biothesiometer (Biomedical Instrument Co., Newbury, Ohio, USA) applying the vibrating probe to the dorsal surface of the great toe and to the external malleolus of both sides.Three determinations were made at each site and the mean values were calculated [14].

Glycated haemoglobin (HbA_{1c}) (minicolumn technique: BIORAD, Richmond, Calif., USA) and albuminuria micro (Micral test Boeringher Mannheim Gmbh, Mannheim, Germany) and macro (Albustix, Ames-Miles Division, Elkhart, Ind., USA) were recorded on the day of the study. An eye examination was performed not more than 3 months before the study.

Table 1. General characteristics of the patients

Group	Age (years)	Diabetes duration (years)	HbA_{1c}
Control ($n = 20$)	51.5 ± 3.4		
Diabetic ($n = 16$)	51.2 ± 1.6	9.5 ± 1.9	7.3 ± 3.4
Diabetic neuropathic ($n = 20$)	56.2 ± 1.4	13.4 ± 2.6	7.9 ± 0.33

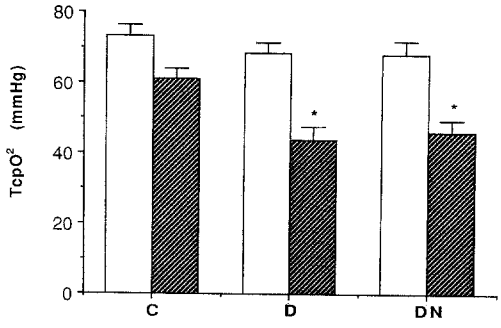

Fig. 1. Foot $TcPO_2$ was significantly reduced in the diabetic (D) and diabetic neuropathic (DN) groups compared to the control (C) group, (*$p < 0.001$), while chest $TcPO_2$ was similar in the three groups. □, chest, ▨, foot

Statistical analysis

All results are expressed as mean ± SEM. Statistics were calculated using a computer (Macintosh Apple) programmed with a standard statistical package (Statview). Analysis of variance, multivariate analysis and linear regression were performed as indicated with p values less than 0.05 considered significant.

Results

Chest $TcPO_2$ was similar in all groups; both diabetic groups had values for foot $TcPO_2$ lower than those observed in group C ($p < 0.001$) (Fig. 1), but there were no differences between these two groups. In control subjects there was a correlation between chest and foot $TcPO_2$ values and age ($r = 0.5$; $p = 0.02$; $r = 0.6$, $p = 0.003$, respectively). In diabetic patients while chest $TcPO_2$ values correlated with age ($r = 0.6$; $p = 0.0001$), foot $TcPO_2$ values did not. There was no correlation between chest and foot $TcPO_2$ and the duration of disease. PaO_2 was similar in all groups with a mean value of 87.9 ± 15.4. The SI values were significantly higher in group DN than in

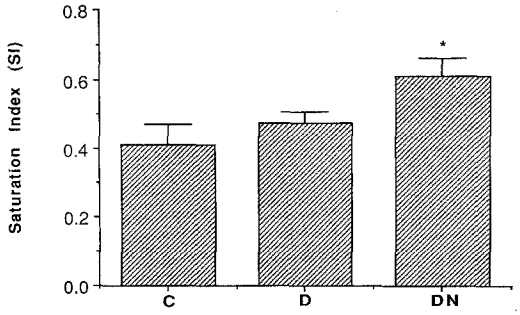

Fig. 2. Saturation index (PvO_2/PaO_2) was significantly increased in the diabetic neuropathic (DN) group compared to the control (C) and diabetic (D) groups (*$p < 0.01$)

groups C and D but there were no differences between groups C and D (Fig. 2). There was also no correlation between SI and TcPO_2 within each group or when all groups were pooled together; SI showed a correlation with duration of disease ($r = 0.462$, $p = 0.002$).

Table 2 shows the cardiovascular autonomic tests and Table 3 the characteristics of peripheral somatic neuropathy, retinopathy and nephropathy for the three groups.

Discussion

Theoretical and experimental analysis of the transcutaneous oxygen measurement indicates that TcPO_2 is a useful method with which to assess the functional status of skin blood flow [15, 16]. Various investigators have already correlated lower limb TcPO_2 with pedal artery pressure [17, 18], signs and symptoms of occlusive arterial disease [19, 20] and prognosis for the healing of amputation sites in patients with foot ulcers [21–23]. Therefore, TcPO_2 is currently being used as a powerful tool for investigation of PVD [24–26].

Several authors have observed a reduction in foot TcPO_2 in diabetic patients [1, 27] and have interpreted these data to be a consequence of PVD. However, Rooke and Osmundson [4] have observed that diabetic patients show lower TcPO_2 values than non-diabetic patients with equivalent degrees of PVD. Therefore, foot TcPO_2 in diabetic patients might be influenced by additional factors, such as autonomic neuropathy, cutaneous microangiopathy etc. Our work was focused on the influence of autonomic neuropathy on foot TcPO_2.

The autonomic nervous system, supplying the arterioles and the A-V shunts with sympathetic adrenergic fibers, directly influences peripheral circulation [28–33]. The consequence of a sympathetic dysfunction is a vasodilatation and an increased flow through the A-V shunts [34], which results in an increased oxygen content in the foot venous blood and therefore in an increased SI [35, 36]. Related to this a "capillary steal" phenomenon has been hypothesized [7]. This could explain the reduced foot TcPO_2 values in diabetic patients without PVD. According to this hypothesis, foot TcPO_2 should be reduced in patients with autonomic neuropathy. However, in our experience foot TcPO_2 was reduced both in diabetic patients with and without autonomic neuropathy. Furthermore, no correlation between SI and foot TcPO_2 values was found. All these observations suggest that sympathetic failure does not influence foot TcPO_2.

The increased oxygen content in the foot venous blood in the group of diabetic patients with autonomic neuropathy is in accordance with the hypothesis of an increased blood flow throughout the A-V shunts in patients with peripheral neuropathy [6, 7, 11, 36], but at the same time our data suggest that a "capillary steal" phenomenon is unlikely, and in any case it does not influence foot TcPO_2. This observation accords with the data from Flynn et al. [37] show-

Table 2. Cardiovascular tests for autonomic function

Group	E: I	LS	VR	PH
Control ($n = 20$)	1.465 ± 0.072	1.275 ± 0.003	1.85 ± 0.023	4.5 ± 0.028
Diabetic ($n = 16$)	1.403 ± 0.073	1.287 ± 0.093	2.06 ± 0.128	7 ± 2.98
Diabetic neuropathic ($n = 20$)	1.193 ± 0.031[a,b]	1.081 ± 0.028[a,b]	1.459 ± 0.101[a,b]	15.55 ± 5.38

E: I, Expiration – inspiration ratio; LS, lying to standing; VR, Valsalva ratio; PH, postural hypotension. [a] Diabetic neuropathic VS Control $p < 0.05$; [b] diabetic neuropathic VS diabetic $p < 0.05$

Table 3. Characteristics of peripheral neuropathy, retinopathy and nephropathy

	VPT (mV)	Retinopathy No/B/P	Nephropathy No/Mi/Ma
Control ($n = 20$)	11.33 ± 2		
Diabetic ($n = 16$)	19.79 ± 4.5	5/8/3	8/8/0
Diabetic neuropathic ($n = 20$)	36.24 ± 2.7[a,b]	1/7/12	6/6/8

VPT, Vibration perception threshold; retinopathy: N = no, B = background, P = proliferative; nephropathy: N = no, Mi = microalbuminuria, Ma = macroalbuminuria. [a] Diabetic nephropathy VS control $p < 0.01$; [b] Diabetic nephropathic VS diabetic $p < 0.05$

ing that capillary flow is maintained in diabetic patients with autonomic neuropathy. Therefore, it seems unlikely that autonomic neuropathy may contribute to the development of foot lesions throughout the induction of foot skin ischaemia. If we exclude the influence of autonomic neuropathy on foot TcPO_2 other conditions such as cutaneous microvascular disorders and barriers to oxygen diffusion could be considered to explain the reduced foot TcPO_2 values observed in diabetic patients. Although our work was not designed to explore these other hypotheses, our data may nevertheless throw some light on these points.

Although thickening of the capillary basement membrane is a common finding in diabetes [38, 39], there is no clear evidence of skin capillary narrowing [40, 41] or occlusion [37, 42, 43]. According to our observations, the influence of structural microangiopathy on foot TcPO_2 is unlikely, because patients with different degrees of microangiopathic complications in other areas (retinopathy and nephropathy) show equivalent foot TcPO_2 values.

The thickening of dermal collagen with increased cross-linking from non-enzymatic glycation could result in a "barrier" to oxygen diffusion [44]. These changes are related to aging [4] and in diabetic patients to the quality of glycaemic control and duration of disease [45]. While this mechanism could explain the relationship between chest TcPO_2 and age in control subjects and diabetic patients, it does not explain why foot TcPO_2 in diabetic subjects does not correlate with age and duration of disease.

None of the hypotheses discussed so far seem to explain the reduced foot TcPO_2 in diabetic patients. An additional hypothesis includes a role for functional abnormalities of the microcirculation [46]. These are considerable in diabetes in general, and not necessarily confined to subjects with obvious neuropathy [47, 48]. According to this hypothesis Breuer et al. [2] observed reduced foot TcPO_2 values even in diabetic patients with a diabetes duration of less than 1 year and free from any detectable microangiopathic complication.

In conclusion, while our data confirm the low foot TcPO_2 values observed in diabetic patients, the clinical impact of this is still unknown. We do not know whether the reduced foot TcPO_2 values observed in the absence of peripheral vascular disease justify the increased susceptibility to foot ulceration observed in diabetic patients. In addition we do not understand the mechanism underlying this phenomenon. Our work was able to exclude a direct role for systemic autonomic neuropathy but does not give information about the local autoregulation mechanisms that, theoretically, could have a role. In our opinion further research in this area is needed to fully understand this finding.

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