Epidural Spinal Cord Electrical Stimulation Improves Microvascular Blood Flow in Severe Limb Ischemia

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Epidural spinal cord electrical stimulation (ESES) was performed on 10 patients with severe limb ischemia due to atherosclerotic disease. Microcirculatory parameters were assessed before and after ESES. Bright field microscopy was used to assess capillary diameters and red blood cell (RBC) velocity in the dorsum of the foot. Fluorescein microscopy was used with intravenously injected sodium fluorescein to study capillary density and sodium fluorescein appearance time in the dorsum of the toe. The systolic ankle/arm pressure ratio and toe pressure measurements were used as macrocirculatory parameters. After ESES, clinical improvement was confirmed by intravital microscopy. Capillary density increased ($p < 0.001$), RBC velocity in capillaries already perfused before ESES increased from 0.054 mm/sec to 0.762 mm/sec ($p < 0.001$), and sodium fluorescein appearance time decreased from 72 to 45 seconds ($p < 0.001$). Capillary diameter did not change significantly so that the increase in RBC velocity may be interpreted as enhanced volume flow. Systolic ankle/arm pressure ratios and digital arterial pressure did not change significantly. The current results show that in patients with severe occlusive arterial disease of the lower limbs, ESES recruits capillaries not perfused in the control situation and enhances skin blood flow, improvements that may explain the beneficial clinical effects of ESES.

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THE SYMPTOMS OF atherosclerotic occlusive arterial disease of the lower limb include intermittent claudication at a relatively early stage of the disease, followed by ischemic rest pain, ulceration, and gangrene as the disease progresses. Vascular surgery is the therapy of choice, but in approximately 20% of the patients with stage IV disease, according to Fontaine, reconstructive surgery is not effective anymore.[1] In these patients, lumbar sympathectomy[2] and conservative treatment[3] generally fail to improve blood supply to the limb and amputation is the last alternative treatment.[3]

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Epidural spinal electrical stimulation (ESES) is a medically accepted therapeutic modality for the control of chronic pain. The best results with ESES have been obtained in patients with intractable low back pain, causalgia, and phantom limb pain.[4] Recently, spinal cord stimulation was also successfully used in patients with ischemic rest pain. Strikingly enough, not only pain relief was achieved, but also healing of ischemic ulcers occurred,[5] suggesting that ESES improves nutritional blood flow. Attempts have been made to delineate these beneficial, clinical effects with the use of the xenon washout technique,[6] ankle pressure measurements,[7,8] or photoplethysmography.[9,10] These macrocirculatory techniques, however, are not sensitive enough to evaluate the effect of ESES on the microcirculatory disturbances, occurring in patients with ulcers and gangrene. In these patients, evaluation of treatment should ideally take place at the level at which the ischemic phenomena occur: the skin nutritional capillaries. Intravital capillary microscopy is a noninvasive method to study the morphologic pattern of the microcirculation[11] and allows the measurement of red blood cell velocity in the skin capillaries, which specifically reflects nutritional blood flow.[12] This technique enables objective evaluation of treatment and can even discriminate respondents from nonrespondents to treatment.[13]

The aim of this study was to evaluate the effects of ESES on microcirculatory blood flow. Morphologic and dynamic capillary microscopy was performed before and after ESES in 10 patients with severe lower limb ischemia.

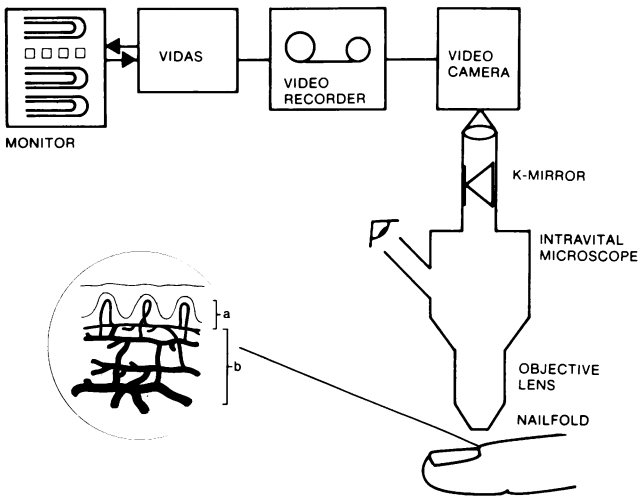


FIG. 1. Schematic representation of the set up for capillaroscopy and of the skin vascular bed, showing the nutritional (a) and thermoregulatory (b) part of skin blood supply.

Patients and Methods

Patients

ESES was performed on 10 patients with occlusive arterial disease of the lower limbs due to atherosclerosis, combined with diabetes in four patients. The mean age of these eight men and two women was 77 years (range: 72–84 years).

Before ESES, patients had vascular reconstructive surgery or sympathectomy without satisfactory result. Angiography, either monoplanar translumbar aortography or biplane selective femoral punction arteriography, showed occluded crural arteries technically unsuitable for reconstructive surgery. Conservative treatment and vasodilating drugs were not effective. All patients had intolerable unilateral rest pain and eight of them had nonhealing ischemic ulcers. The only possible therapeutic alternative was limb amputation.

Protocol

The first patient was treated with ESES 15 months ago; the last patient was treated 2 months ago. Because of the short follow-up period, only the acute effects of ESES on vascular blood flow are presented. The following macro- and microcirculatory parameters were investigated 1 day before and 1 day after ESES.

Macrocirculation

The systolic ankle/arm pressure index, expressed as a percentage, was determined by dividing the systolic pressure, as measured over the posterior tibial or the dorsal pedal artery, by the systolic brachial artery pressure and multiplying this ratio by 100%. The pressure measurements were made with a bidirectional continuous wave Doppler instrument with a zero-crossing circuitry.

Photoplethysmography was used to measure the systolic pressure in the digital arterial system of the toe, using a pressure cuff around the proximal phalanx with a width of 1.5 cm. The systolic pressure was expressed in mmHg.

Microcirculation

Nutritional capillary blood flow and capillary morphology were studied by means of intravital microscopy with objectives L4× (numerical aperture NA = 0.04) and L10× (NA = 0.22). Figure 1 schematically represents the set up with a magnification of the skin microcirculation: arterioles and arteriovenous anastomoses, which form the thermoregulatory part of skin blood flow, and skin capillaries, which are responsible for the nutritional part of skin blood flow. The foot of the sitting patient was positioned on the stage of the microscope and fixed in a mass of clay. A drop of paraffin oil was applied to the nailfold and skin to minimize reflections. The technique of capillary microscopy has been described in detail before.[14,15] Essentially, the system (Fig. 1) consists of the microscope, which is connected with a television monitor through a low light level television camera. For offline analysis the images were stored on a videotape recorder. Capillaries were randomly chosen in the nailfold and dorsum of the skin of the foot to determine the following morphologic and dynamic parameters: (1) the density of the capillary loops, as measured with objective 4×. The density was expressed as the number of capillary loops per square millimeter. (2) The diameter of the capillary loop, using the objective 10×. Diameters were expressed in micrometers. (3) Capillary red blood cell (RBC) velocity, as measured with a video flying spot method.[16] In this technique, a spot moving over the videoscreen is synchronized with the moving red blood cells or plasma gaps. The advantage of this system is that very low RBC velocities can be measured accurately. (4) Appearance time of intravenously injected sodium fluorescein and number of capillaries perfused with this dye. Two milliliters of 10% sodium-fluorescein were injected intravenously, where on the arrival of the dye in the skin of the foot, was assessed with the use of a fluorescein microscope filter. The time between injection of the dye and arrival in the foot was defined as the appearance time, expressed in seconds. Furthermore, the number of capillaries filled with sodium-fluorescein was determined and expressed in number per square millimeter. Since sodium-fluorescein binds to plasma proteins, these capillaries filled with sodium-fluorescein do not only represent blood

perfused capillaries, but also the capillaries perfused with plasma.

Surgical Procedure

Under local anesthesia, a vertical incision parallel to the spinal column was made. Through a Tuohy needle, an electrode was introduced into the epidural space at the level of L3–L4 and placed in the midline approximately at the level of T10. This was performed under x-ray control. The lead was manipulated until the patients experienced pleasant paresthesias extending down into both legs. Patients were stimulated either by external stimulation or by an internal device that was implanted in a subcutaneous pouch connected to the epidural electrode via a subcutaneous extension (Medtronic Inc., Minneapolis, MN).

Bipolar stimulation was performed with a pulse width of 0.2 msec and a frequency of 120 Hz. The amplitude varied between 4 and 9 V, depending on the patient's subjective feeling of comfortable paresthesias.

Statistical Analysis

In the tables, the data are presented as mean values and standard deviations. The Student's t-test was applied to evaluate the differences before and after ESES.

Results

Subjective Findings

Nine of the ten patients with severe rest pain showed immediate pain relief after spinal cord stimulation. In one patient pain was reduced, but displacement of the electrode caused unpleasant painful paresthesias. After a few weeks the electrode was removed. There was no difference in subjective findings between patients with and without diabetes. During the follow-up period, amputation was necessary in three patients, including the patient in whom ESES was stopped. These patients had gangrene before ESES. In the other five of the eight patients with ischemic ulcers, complete healing occurred in two patients and an improved tissue integrity was observed in three patients.

Objective Findings

Macrocirculation. Before ESES the mean systolic ankle/arm pressure index was 32%, which did not change after treatment (Table 1). The systolic toe pressure before treatment was 9 mmHg and increased to a mean value of 19 mmHg after ESES. This difference, however, was not statistically significant.

Microcirculation. Morphologic investigation of the skin capillaries revealed that both with and without sodium fluorescein the number of perfused capillaries increased significantly ($p < 0.001$) after ESES (Table 2). In Figure 2 the capillary bed filled with sodium-fluorescein is shown before and after stimulation. The obvious avascular areas before treatment are perfused after ESES. Skin capillary diameter (15.7 μm) did not change after treatment.

Mean RBC velocity in the control situation was 0.054 mm/sec. One day after spinal cord stimulation, RBC velocity increased enormously in all patients to a mean value of 0.762 mm/sec ($p < 0.001$). The appearance time of sodium-fluorescein in the capillary bed significantly decreased in all patients ($p < 0.001$).

TABLE 1. *Macrocirculatory Parameters Before and After ESES**

	Before	After	Significance
Systolic ankle/arm pressure index (%)	32 ± 14	37 ± 14	NS
Systolic toe pressure (mmHg)	9 ± 16	19 ± 23	NS

* Mean ± SD.
NS = not significant.

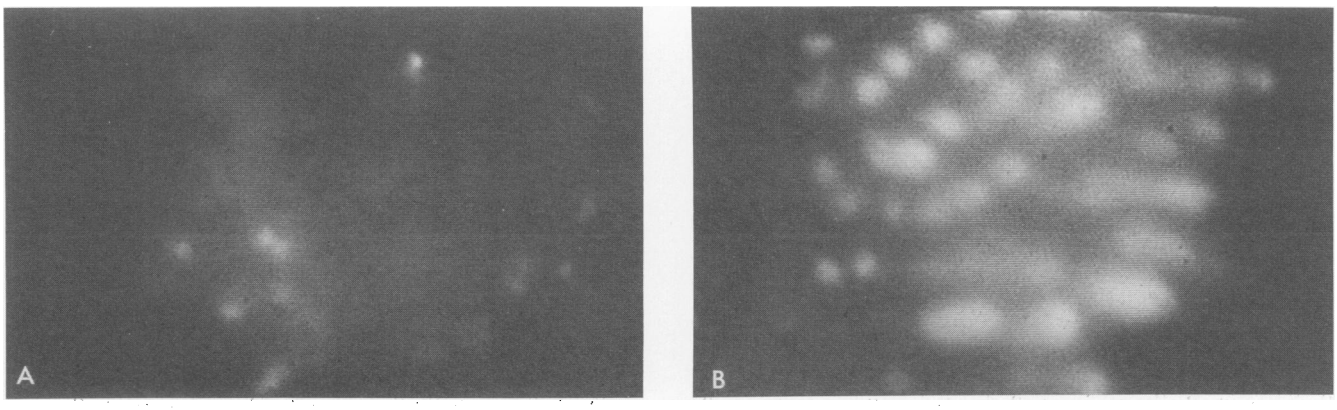
Discussion

In this study, skin capillary microscopy was shown to be a noninvasive method to evaluate microcirculatory changes induced by spinal cord stimulation. After ESES, the number of skin capillaries perfused and skin capillary RBC velocity significantly increased. The increase in velocity may be interpreted as an increase in skin blood flow rate because capillary diameter did not significantly change under these circumstances. The increase in skin capillary density and flow rate likely explain the observed clinical improvement and ulcer healing in patients with occlusive arterial disease treated

TABLE 2. *Microcirculatory Parameters Before and After ESES**

	Before ESES	After ESES	Significance
Skin capillary density (n/mm^2)	12 ± 6	30 ± 5	$p < 0.001$
Skin capillary diameter (μm)	15.7 ± 1.8	15.5 ± 1.5	NS
Red blood cell velocity (mm/sec)	0.054 ± 0.014	0.762 ± 0.205	$p < 0.001$
Sodium-fluorescein perfused capillaries (n/mm^2)	20 ± 4	44 ± 5	$p < 0.001$
Sodium-fluorescein appearance time (sec)	72 ± 15	45 ± 9	$p < 0.001$

* Mean ± SD.
NS = not significant.



FIGS. 2A and B. Skin capillary bed after injection of sodium-fluorescein before (A) and after (B) ESES.

with ESES. Theoretically, the increase in skin perfusion can be caused by improved proximal arterial inflow, an idea supported by the significant decrease in sodium-fluorescein appearance time. The enhanced flow rate, however, did not result in a significant increase in ankle and digital arterial pressure, which might be explained by still fully dilated arterioles in this situation resulting in a "sink" for flow. An alternative explanation for the increase in nutritional skin blood flow could be redistribution of flow from muscle or bone towards the skin. ESES, however, was found to enhance skeletal muscle blood flow[17] so that shunting of blood from muscle to skin is less likely.

The patients in this study were all in the last phase before amputation. Seven of the ten patients reported long-term subjective improvement after spinal cord stimulation and were free of pain, whereas in three patients amputation was necessary. These beneficial effects are in agreement with the observations of Augustinsson et al.,[18] who used ESES in patients with ischemia based on atherosclerosis, Buerger's disease, and severe vasospastic disorders. Only 38% of the stimulated atherosclerotic patients had amputation compared with 90% in a comparable group of unstimulated patients. The amputation rate was highest in patients with ulcers and gangrene before ESES, suggesting that the treatment has no limb-saving effect when there is an established partial gangrene, which is in concurrence with the results of Broseta et al.[7]

The mechanisms by which ESES exerts pain relief and improved blood flow are still unclear. Pain is a symptom of tissue damage, caused by stimulation of A-delta and C fibers, transmitted to the cells of the substantia gelatinosa, the dorsal-column fibers, and the first central transmission (T) cells in the dorsal horn. In their "gate control theory" Melzack and Wall[19] propose that pain is determined by interaction between these three transmitting systems. The theory assumes that stimulation of the larger A fibers finally results in inhibition of the T cells. Consequently, these T cells do not react anymore to pain impulses *via* the smaller fibers. The idea of dorsal root electrical stimulation is based on the activation of the larger A fibers, leading to blockade of pain stimuli. Pain relief may release the reflex vasoconstriction that is known to occur in response to pain. Whether the sympathetic nervous system is involved is unclear. Augustinsson et al.[20] observed autonomic changes after stimulation in both patients with and without pain, raising the question whether the pain-reducing effect and the autonomic effects are a consequence of or caused by a common mechanism or two parallel phenomena. According to Melzack and Wall,[19] autonomic pathways in the intermediate columns of the grey area regulate the degree of peripheral vasoconstriction. Current spread of electrical stimulation into this area theoretically releases segmental spinal reflexes, inhibiting sympathetic fiber discharge to vessels in the extremities. Owens et al.[21] demonstrated increased infrared emission after application of nerve electrical stimulation, postulating the indirect evidence of cutaneous vasodilatation and hence, decreased sympathetic tone. This enhanced skin temperature indicates that not only nutritional flow, but also arteriovenous shunt flow increases after ESES.

Another approach to vasodilatation after electrical stimulation is described by Hilton and Marshall.[17] They demonstrated vasodilatation in the cat gastrocnemius muscle after dorsal root stimulation and postulated that this effect is due to antidromic stimulation of small diameter fibers. This dilatation was unaffected by sympathetic blocking agents, but greatly reduced by prostaglandin inhibitors. They concluded that activity in the afferent fibers of skeletal muscle produces an increase in muscle blood flow, mediated by the release of prostaglandins in muscles.

In conclusion, epidural spinal cord stimulation improves skin nutritional blood flow in patients with severe lower limb ischemia, leading to wound healing and possible limb salvage. Therefore, ESES is a promising

treatment in this group of patients. Especially with our forthcoming ageing population it is extremely important to perform prospective clinical and physiologic studies to clarify the indications and to investigate the mechanisms involved.

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