Epidural Electrical Stimulation in Severe Limb Ischemia

Pain Relief, Increased Blood Flow, and a Possible Limb-saving Effect

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Peripheral vascular disease of the extremities causes ischemic pain and, at times, skin ulcerations and gangrene. It has been suggested that epidural spinal electrical stimulation (ESES) could improve peripheral circulation. Since 1978 we have used ESES in 34 patients with severe limb ischemia; all had resting pain and most had ischemic ulcers. Arterial surgery was technically impossible. Twenty-six patients had arteriosclerotic disease, one had Buerger's disease, and seven had severe vasospastic disorders. Ninety-four per cent of the patients experienced pain relief. ESES healed ulcers in 50% of those with preoperative nonhealing skin ulcerations. Seventy per cent of the patients showed improved skin temperature recordings. Only 38% of the stimulated arteriosclerotic patients underwent amputations during a mean followup period of 16 months, as compared to 90% of a comparable group of unstimulated patients. ESES is very promising in severe limb ischemia where reconstructive surgery is impossible or has failed.

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PERIPHERAL ARTERIAL INSUFFICIENCY due to atherosclerosis is a frequent condition in elderly people. In most cases, the symptoms are relatively mild and remain stable.[1,2] However, in approximately 10% of the patients with peripheral arterial insufficiency, the disease will progress to gangrene within a period of 5 to 10 years.[3] In the majority of these cases, vascular reconstruction will save the limb, but amputation will be needed in the remaining cases. In the group of patients where vascular surgery is impossible or has failed, various methods to accomplish pain relief and improve blood flow have been tried, but so far no method has achieved general acceptance.[4]

Epidural spinal electrical stimulation (ESES) offers a new possibility in the treatment of these patients. ESES is used to relieve pain in patients with chronic pain conditions and to improve motor functions in patients with partial lesion of the spinal cord. These patients sometimes remark that their lower extremities feel warmer with the stimulation than without it, and a reduction or disappearance of discoloration of the skin is also noted.

In 1976, Cook et al.[5] used ESES in nine patients with peripheral vascular disease of different etiologies and showed skin healing of chronic leg ulcers by stimulation. The authors suggested that the effect of stimulation was caused by activation of vasodilator fibers in the posterior roots, but considered that a modification of the central spinal cord autonomic pathways could have produced similar changes.

In 1983, Tallis et al.[6] reported on ten patients with severe intractable symptoms of arterial disease in the legs receiving spinal cord stimulation. Six out of ten patients showed clinical improvement. The mean claudication distance, as well as exercise tolerance on the bicycle ergometer, increased. The authors suggested that the effect was due to antidromic stimulation of the central processes of the first-order sensory neurons.

Since 1978 we have used ESES in 34 patients with severe limb ischemia of different etiologies in order to study the clinical effect. Our goal was to find objective changes in peripheral circulation that support the clinical beneficial impression of ESES. Our aim also was to study whether ESES had a limb-saving effect.

Patients and Methods

Patients

Thirty-four patients were included in the study. The characteristics of the patients are presented in Table 1. The average age was 64 ± 14 years (S.D.); there were 21 men and 13 women. Twenty-six patients had arterio-

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TABLE 1. *Characteristics of Patients Treated with ESES*

Patient No.	Follow-up Period (Months)	Age	Sex	Disease	Previous Vascular Reconstruction	Intolerable Resting Pain	Skin Ulcer Before ESES	Gangrene Before ESES	Systolic Toe/Finger BP Before ESES (mmHg)	During treatment: Pain Relief	During treatment: Amputation (Months to Amputation)	During treatment: Mortality (Months to Death)
1	24	75	F	AS*	0	+	+	0	20	+++	–	
2	20	72	M	AS	+	+	0	0	0	0	+ (1)	
3	13	67	M	AS	+	+	0	0	35	+	–	+ (13)
4	25	63	M	AS	+	+	+	0	0	++	–	
5	1	77	F	AS	0	+	+	+	0	+	+ (1)	
6	24	72	F	AS	0	+	+	0	0	0	+ (7)	+ (7)
7	1	68	M	AS	0	+	+	+	0	+	+ (1)	
8	24	77	M	AS	+	+	+	0	10	++	–	
9	8	76	M	AS	0	+	+	0	ulcer¶	+	+ (8)	
10	21	65	M	AS	0	+	0	0	50	+	–	
11	17	74	M	AS	0	+	+	0	5	+++	–	+ (17)
12	41	65	F	AS	0	+	+	0	ulcer¶	+	+ (24)	+ (41)
13	14	75	M	AS	+	+	+	0	0	+	–	+ (14)
14	9	60	M	AS	+	+	0	0	50	++	–	
15	8	62	M	AS	+	+	+	0	0	++	–	
16	7	69	M	AS	+	+	+	+	6	++	+ (2)	
17	9	75	M	AS	0	+	+	0	0	+++	–	
18	1	79	F	AS	+	+	0	0	26	+++	–	
19	1	78	M	AS	0	+	0	+	0	++	–	
20	1	77	M	AS	0	+	+	+	0	++	+ (1)	
21	1	57	F	AS	+	+	+	0	0	++	–	
22	6	75	F	D†	0	+	+	+	0	+	+ (6)	
23	21	75	M	D	+	+	+	0	0	+	–	
24	36	70	M	D	0	+	+	0	20	++	–	
25	3	49	M	D	0	+	+	+	20	++	+ (3)	
26	5	65	M	D	+	+	+	0	35	++	–	+ (5)
27	4	50	M	B‡	0	+	+	0	12	+	–	
28	78	44	M	VSD§	0	+	+	0	10	+++	–	
29	21	51	F	VSD	0	+	+	+	0	+++	–	
30	19	62	F	VSD	0	+	0	0	90	+++	–	
31	38	41	M	VSD	0	+	+	0	20	+++	–	+ (38)
32	1 Month, then lost at follow-up	39	F	VSD	0	(+)	0	0	–			
33	8	21	F	VSD	0	+	0	0	60	+++	–	
34	11	42	F	VSD	0	+	0	0	59	+	–	

*AS = Arteriosclerosis.
† D = Diabetes.
‡ B = Buerger's disease.
§ VSD = Vasospastic disease.
¶ Skin ulcers made recordings impossible.

sclerotic disease, five of whom were diabetic. One patient had Buerger's disease. The mean age in this group was 70 years (range *49–78*). Angiography was performed in all patients and vascular surgery was considered impossible because of very advanced disease of the crural arteries. Arterial blood pressure of the first toe averaged 12 ± 4 mmHg in the patients with arteriosclerosis, and it was zero in 50% of these patients. Twenty-three per cent of these patients already had partial gangrene when ESES was started. All arteriosclerotic patients had intolerable resting pain, and most (78%) of them had nonhealing skin ulcers. The only therapeutic alternative to ESES in these 27 patients was a limb amputation. Prior surgery had failed in many of these patients (46%).

Seven patients had vasospastic disorders. The average age in this group was 43 years (range 21–62). All patients with vasospastic disease had intolerable pain, and three patients had nonhealing ulcers in the fingertips or toes. Sympathectomy (3 patients) and/or conservative treatment had failed. Informed consent was obtained from all patients.

Methods

Systolic blood pressure of the first toe or the thumb was measured by the strain gauge technique. Continuous skin temperature measurement was performed in a temperature-stable room on all fingers or toes at rest and for 40 minutes after a period of cooling. During the temperature measurement, indirect body heating was

TABLE 2. *Effect of Spinal Cord Stimulation on Pain Relief*

Disease	No Improvement No. Patients Per cent	Fair† No. Patients Per cent	Good† No. Patients Per cent	Excellent† No. Patients Per cent	Total No. Improved Per cent
AS*	2 (10%)	7 (33%)	9 (43%)	3 (14%)	19/21 (90%)‡
D	—	2 (40%)	2 (40%)	1 (20%)	5/5 (100%)
B	—	1	—	—	1/1
VSD	—	1 (14%)	1 (14%)	5 (72%)	7/7 (100%)
AS + D + B + VSD	2 (6%)	11 (32%)	12 (35%)	9 (27%)	32/34 (94%)‡

* See Table 1 for abbreviations.

† Pain relief was considered fair when there was a reduction of pain of <33% on the scale 0–100, good when it was reduced 34–66% and excellent 67–100%.

‡ $p < 0.01$ (One-sided test using the binomial distribution).

applied. The accuracy of the thermistor bridge is better than 0.5°C.

Follow-up

One patient was lost to long-term follow-up, and is presented in Table 1 to illustrate pain relief (in this case, within 30 days from surgery). The remaining patients (N = 33) were followed until the end of the study or until their death. They were examined on an outpatient basis at least four times a year. The mean follow-up period was 15 months (range 1–78 months). The follow-up included a physical examination and measurement of ulcerations. The use of analgesics was recorded, as well as the patient's opinion of the degree of pain. All patients, when possible, underwent recordings of the systolic toe pressure and skin temperature after local cooling. These measurements were impossible in a number of patients because of ulcerations or distal gangrene. The measurements were performed with and without a prior period of 24 hours of spinal stimulation. Pain relief was estimated from the patient's opinion of the degree of pain on a scale of 0 to 100 before and after implantation of the electrode. Concerning amputations, the medical records of a comparable group of unstimulated patients were examined. They were all admitted between 1976 and 1977 (*i.e.*, before this study). During this period, they were the only patients with severe rest pain due to arteriosclerosis and diabetes who, for technical reasons, were considered impossible to restore with vascular surgery.

Statistical methods. Wilcoxon's rank sum test, Student's t-test, and binominal distribution test were used.

Operative Technique

The operation, performed under local anesthesia, is the same as when ESES is used in patients with chronic pain conditions. An electrode was introduced epidurally *via* a Touhy needle. The electrode was manipulated under fluoroscopic control in the midline, or slightly lateral to the midline, referring to the affected limb. When the legs were affected, the epidural space was punctured at the level of L–3, and the tip of the electrode was placed at approximately the T–10 vertebral level. Corresponding levels when the arms were affected were T–3 and C–5, respectively. The radio receiver was implanted in a subcutaneous pouch just above one of the costal arches and was connected to the epidural electrode *via* a subcutaneous extension. Prophylactic antibiotics were administered for 1 week.

Two commercially available electrical devices of equal function were used in this study (Avery Laboratories, Farmingdale, NY and Medtronic, Inc., Minneapolis, MN).

One to 3 days after the operation, the patient was taught how to use the stimulator. The patient used a radiotransmitter connected to an antenna that was applied to the skin over the subcutaneously-placed radio receiver. The electrical parameters were: frequency 100 Hz, pulsewidth 0.2 ms. A voltage high enough to give comfortable paresthesias in the affected limb or limbs was chosen. Most patients used the stimulator during the day in 2-hour periods with 2-hour intervals, but some used it continuously.

Results

The results are summarized in Tables 2 to 6. Seven patients (21%) died during the follow-up period, six of whom belonged to the arteriosclerotic/diabetic group. Six died from myocardial infarction and one died from malignant disease.

Pain Relief

Ninety-four per cent of the patients experienced reduction of their pain during stimulation (Table 2). In patients with arteriosclerosis and diabetes the relief of pain was adequate, and in the vasospastic group the pain relief was almost total. There were two nonresponders in the arteriosclerotic group. Twenty-two patients

TABLE 3. *Effect of Spinal Cord Stimulation on Ischemic Ulcer Healing (within 12 Months)*

Disease	No Effect No. Patients Per cent	Improved Healing No. Patients Per cent	Ulcer Healed No. Patients Per cent	Total Improved Per cent of Total
AS*	8 (50%)	4 (25%)	4 (25%)	8/16 (50%)
D	4 (80%)	0	1 (20%)	1/5 (20%)
AS + D	12 (57%)	4 (20%)	5 (23%)	9/21 (43%)
VSD	0	0	3	3/3 (100%)
AS + D + VSD	12 (50%)	4 (17%)	8 (33%)	12/24 (50%)

* See Table 1 for abbreviations.

with arteriosclerosis and diabetes needed morphine derivatives to control pain prior to ESES. The morphine derivatives in 20 of these patients could be omitted during ESES therapy.

Skin Ulcers

Twenty-four patients (71%) had nonhealing skin ulcers prior to ESES. Twelve of these (50%) had total healing or major improvement of the ulcers within 1 year of ESES (Table 3). All vasospastic patients with skin ulcers healed, but only one of the five diabetics.

Amputation

Ten patients, all arteriosclerotics or diabetics, underwent amputations during the follow-up period. Amputation was necessary in all six patients with gangrene prior to ESES, but in only four (20%) of the 20 patients with no gangrene prior to ESES. Only one patient without a skin ulcer prior to ESES was amputated, as opposed to nine out of 20 (45%) with a skin ulcer. Three of the ten patients underwent amputation of the forefoot; seven underwent the usual below-the-knee amputation (Table 4). In summary, 38% of the arteriosclerotics and diabetics on ESES therapy were amputated, as compared to 90% in a comparable group of unstimulated patients.

Objective Measurements

There was an average increase of 8 ± 3 (SEM) mmHg of the systolic toe pressure in response to ESES in patients with arteriosclerosis and diabetes. For thumb pressure in the vasospastic patients, the corresponding increase was 19 ± 2 mmHg (Table 5). Skin temperature after local cooling increased faster in 14 of 20 patients after application of ESES (Table 6).

There was slight correlation ($r = -0.49$) between the blood pressure of the first toe prior to ESES and amputation, but there was no correlation ($r = +0.07$) between the toe pressure and pain relief.

Complications and Side-effects

No intraoperative or immediate postoperative complications occurred. In one patient, a local infection around the receiver occurred 2 months after surgery and necessitated removal of the whole system. The patient healed without sequelae. Electrode migration or lead break occurred with loss of stimulation-produced paresthesias in six patients. After repositioning of the electrode or lead exchange, the system functioned properly again. The electrode was accidentally inserted subdurally in one patient. Stimulation gave adequate paresthesias but, 2 months after the operation, the patient complained of

TABLE 4. *Amputations*

Disease*	Amputated Patients Per cent	Time to Amputation Months	Not Amputated No. Patients Per cent	Follow-up Nonamputated Patients Months
AS (N = 20)	8 (40%)	1, 1, 1, 1, 2, 7, 8, 24† (Average = 6 ± 3)	13 (60%)	1, 1, 1, 4, 8, 9, 20, 23, 23, 24, 27, 34, 35† (Average = 16 ± 3)
D (N = 6)	2 (33%)	6,3	3 (60%)	5, 21, 36 (Average = 21)
AS + D (N = 26)	10 (38%)		16 (62%)‡	
"Controls"	9 (90%)	1, 1, 1, 3, 3, 6, 7, 10, 10 (Average = 5 ± 1)	1 (10%)	84

* See Table 1 for abbreviations.

† The four patients amputated within the first month all had a partial gangrene when starting ESES.

‡ $p < 0.02$ compared to controls.

TABLE 5. *Alteration of Systolic Blood Pressure of the First Toe (AS) or First Finger (VSD) in Response to ESES (mmHg)*

Disease	Systolic Blood Pressure	
	Before ESES	Response to ESES
Arteriosclerosis		
Affected leg (N = 10)	10 ± 6	+8 ± 4*
Opposite leg (N = 10)	40 ± 7	+9 ± 4*
Total (N = 20)	23 ± 5	+8 ± 3†
Vasospastic Disease		
Affected arm (N = 4)	57 ± 24	+19 ± 4
Opposite arm (N = 3)	67 ± 12	+18 ± 1
Total (N = 7)	61 ± 14	+19 ± 2*

* $p < 0.05$.
† $p < 0.01$.

headache during stimulation; therefore, the electrodes were removed in spite of a good clinical result.

Discussion

The most important symptom in patients with severe limb-threatening ischemia is the pain. These patients suffer from pain day and night, and it is impossible for them to live a normal life. Analgesics give short-term relief, if any. The pain, combined with lack of sleep, makes the patient exhausted; some of these patients consider suicide. Under these circumstances, amputation is often the only alternative for relief of the intractable pain when arterial surgery is impossible.

One of the main advantages of spinal cord stimulation has been the beneficial effect on pain. Thus, only two patients out of the 34 did not experience any relief of pain during stimulation. The pain relief was most effective in vasospastic disease, indicating that ESES, in addition to suppressing pain, also reduces the vasospasm. These patients also showed the most pronounced increase in blood pressure of the first toe or thumb during stimulation. A normalization of skin temperature after local cooling was also seen.

All but two patients with arteriosclerosis obtained pain relief. Surprisingly in these patients a slight, but significant increase in local systolic blood pressure occurred during stimulation, and an increase of skin temperature was obtained in the majority. Ischemic nonhealing skin ulcers due to vasospastic disease all healed within a couple of months, even extensive and deep ulcerations. Even in the arteriosclerotic group, the stimulation seemed to promote ulcer healing in about half of the cases.

TABLE 6. *Skin Temperature Recordings After Local Cooling During Spinal Cord Stimulation*

Disease*	No Improvement No. Patients	Improved No. Patients	Skin Temperature Returned to Normal No. Patients
AS + D (N = 16)	5	10	1
VSD (N = 4)	1	1	2

* See Table 1 for abbreviations.

In published reports of the natural course of patients with severe limb ischemia, it is shown that in patients with severe pain at rest and nonhealing ischemic ulcers, amputation will be needed in 65 to 70% of the cases within a year if no effective treatment is instituted.[7] This is in accordance with our own experiences. From 1976 to 1977, the ten "control" patients were treated conservatively for severe limb ischemia because surgical reconstruction was impossible. Their ages and the severity of their symptoms did not differ from those of the patients on ESES therapy in the present study. Nine of the ten "control" patients (90%) underwent amputation within 10 months. In this series, it was possible to avoid amputation in 62% of the cases during a mean observation time of 16 ± 3 (SD) months. This indicates that ESES has a limb-saving effect. In patients without partial gangrene prior to ESES, the limb-saving rate was 80%.

Our experience has been that any patient with normal mental capacity can very quickly learn to use the equipment and to control the strength of the signal needed to obtain adequate paresthetic sensation in the affected extremity or extremities.

In a few patients, we followed skin temperature changes with a thermocamera. It was noticed that, if some of these patients had not used ESES 24 hours before thermocamera examination, the immediate effect of electrical stimulation was a decrease of skin temperature that lasted for 30 to 60 minutes, whereupon an increase of the skin temperature occurred. This pattern has certain similarities to that of an intraarterial injection of reserpine, which depletes the neurotransmitter noradrenaline from the sympathetic nerve endings, resulting in an immediate vasoconstriction followed by a vasodilation.[8] This is interesting, since it is shown that prostaglandins of the E-type inhibit the release of noradrenaline from adrenergic nerve terminals,[9] which would act to diminish vasoconstriction if there is a sympathetic tone. Dorsal root stimulation in the cat induces vasodilation in the calf muscles; this effect is blocked by indomethacin, a prostaglandin synthesis inhibitor.[10] This might indicate that the effects of ESES are due to local prostaglandin release. Prostaglandins, *e.g.*, PGE, are known to have a favorable influence on limb ischemia when administered intraarterially.[11]

It is well-known from clinical experience that even minor improvement in perfusion pressure is important

in the severely ischemic limb. Thus, many patients experience pain relief by hanging the foot out of the bed at night and, thus, adding a few mmHg hydrostatic pressure to the limb. It has been shown with xenon washout technique that the addition of this small hydrostatic pressure increases the perfusion of the skin.[12] Hence, it is probable that the small increase in distal systolic pressure obtained in our patients is concomitant with a better distal perfusion in these critically ischemic limbs. When a part of an extremity is cooled down in a normal patient, a vasospasm is induced lasting for 5 to 10 minutes, whereupon a reactive hyperemia occurs, and the temperature quickly returns to normal. In patients with severe limb ischemia, this immediate response to cooling due to vasospasm does not occur or is much less marked, and the temperature increases gradually toward room temperature with no sign of reactive hyperemia. In a previous report, we have shown that intramuscular injection of chlorpromazine in patients with severe ischemia results in an increase of the skin temperature, and even causes a faster return of skin temperature after cooling.[13] This effect is very similar to that produced by ESES.

The mechanisms by which ESES exerts its effects are still very unclear. Generally, the understanding of ESES in pain conditions is based on a theory of segmental pain inhibition postulated by Melzack and Wall[14] in their gate-control theory. There is additional evidence that electrical stimulation may act by releasing endorphins and by inhibiting transmission of noxious stimuli on various levels.[12]

The associated or possible specific effect of electrical stimulation on autonomic functions has currently been presented,[15] but its neurophysiological basis has not been explored. Thus, it is not known if the pain-reducing effect and the autonomic effects are due to a common mechanism or if they are two parallel phenomena. If the increase of local blood pressure and the increase of skin temperature reflect changes in sympathetic activity, this might be a consequence of pain reduction. It is assumed that the pain-conducting system channels activity to sympathetic neurons. This connection implies that an increased noxious input results in an increased sympathetic outflow, even in patients with arterial insufficiency. Such pain-induced sympathetic overstimulation may lead to further abnormalities of the circulation, increased ischemic damage, and further activation of nociceptors, etc. It follows that if the noxious signal is blocked by ESES, the sympathetic tone will decrease, resulting in dilatation of the vessels and increased blood flow in the affected areas. This is evidently a local effect, since there was no increase of the systemic blood pressure that could explain the local changes.

The second alternative implies that ESES reduces pain but influences autonomic systems by a separate mechanism. This possibility is not unrealistic. Elicitation of visceral effects by stimulation is well-documented in animal experiments. A recent study has shown that low frequent (3 Hz) stimulation of the sciatic nerve gives a significant decrease of the blood pressure in hypertensive rats.[16] This effect can be reversed by naloxone, indicating that the effect is exerted *via* neuronal system using endorphins. In man, transcutaneous electrical stimulation applied suprapubically can increase the functional bladder capacity in patients with interstitial cystitis.[17] In patients with angina pectoris, transcutaneous electrical stimulation on the chest has been shown to improve myocardial perfusion.[18] Thus, there are reasons to assume that electrical stimulation can influence the function of various organs, probably by changes in reflex mechanisms and their control from higher centers. Sometimes this effect can be elicited without influencing the pain-transmitting system.

If one accepts the idea that electrical stimulation can separately block the sympathetic outflow, the explanation for this effect is still unclear. Three possible mechanisms may be considered. First, it has been shown in animal experiments that an antidromic activation of C-fibers in the posterior roots increases the local skin blood flow. This effect is analogous to the axon-vasodilatator reflex.[19] Such a mechanism seems, however, not possible in the present situation because the patients did not use a stimulation strength high enough to activate the afferent C-fibers. Further, the patients had no sensation of nociceptor fiber discharge. Second, the stimulation might activate ascending pathways to the supraspinal autonomic centers responsible for a more general vasomotor fiber adjustment. If this had been the case, one would have expected a more generalized influence and not only the local changes. Third, the stimulation may release segmental spinal reflexes, inhibiting sympathetic fiber discharge primarily to the vessels in the extremities. This seems to be the most plausible explanation.

In this study, when there already was an established gangrene prior to ESES, stimulation could give pain relief, but none of these limbs were saved. The amputation rate was lowest (16%) in patients without skin ulcer or gangrene prior to ESES. A systolic blood pressure of the first toe of zero, or close to zero, had some predictive value regarding the limb-saving effect, although many of these limbs were saved; however, a low value did not correlate with the pain-relieving effect. Hence, the method can be recommended regardless of the blood pressure of the first toe, but has no limb-saving effect when there is an established partial gangrene. ESES can be recommended in severe vasospastic disease

especially to those with nonhealing skin ulcers. We find epidural electrical stimulation very promising in patients with severe limb ischemia where other therapeutic alternatives have failed. We believe that the main effect is the pain relief, thus making life more tolerable for the patient, but epidural electrical stimulation also seems to have sympatholytic and wound healing effects and can thus be limb-saving.

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