Effect of Transcutaneous Electrical Nerve Stimulation on Coronary Blood Flow

Anoop Chauhan, MRCP; Paul A. Mullins, MRCP; Suren I. Thurasingham, MRCP; Ged Taylor; Michael C. Petch, MD, FRCP; Peter M. Schofield, MD

Background Although neurostimulation has been shown to be of benefit in angina pectoris, the exact mechanism of its action is not clear. This study was performed to examine the effect of transcutaneous electrical nerve stimulation on coronary blood flow.

Methods and Results The effect of transcutaneous electrical nerve stimulation was studied in 34 syndrome X patients (group 1), 15 coronary artery disease patients (group 2), and 16 heart transplant patients (group 3). Coronary blood flow velocity (CBFV) in the left coronary system was measured at rest and after a 5-minute stimulation period with a Judkins Doppler. There was a significant increase in the resting CBFV in group 1 (from 6.8±4.1 to 10.5±5.7 cm/s, \(P<.001\)) and group 2 (from 6.8±4.1 to 10.5±5.7 cm/s, \(P<.001\)). However, there was no significant change in the resting CBFV in group 3. There were no significant changes in the coronary arterial diameters as a result of neurostimulation. There was a significant decrease in the epinephrine levels in group 1 (from 79.6±17.8 to 58.5±17.5 ng/L, \(P=.01\)) and group 2 (from 102.2±27.2 to 64.1±19.1 ng/L, \(P=.01\)).

Conclusions Transcutaneous electrical nerve stimulation can increase resting coronary blood flow velocity. The findings suggest that the site of action is at the microcirculatory level and that the effects may be mediated by neural mechanisms. (Circulation. 1994;89:694-702.)

Key Words • transplantation • coronary disease • norepinephrine

During the last decade, electrical neurostimulation has developed as a means of therapy for control of pain and has been shown to be useful in a variety of chronic painful conditions.\(^1\)\(^-\)\(^3\) Recently, it has also been shown to have a beneficial effect in the treatment of ischemic pain.\(^4\)\(^-\)\(^7\) Transcutaneous electrical nerve stimulation (TENS) treatment has also been shown to be of benefit in angina.\(^8\)\(^-\)\(^11\) In patients treated with TENS there was a reduction in chest pain, an increase in work capacity, and a decrease in ST-segment depression at a comparable workload. This improvement persisted during the posttreatment follow-up period of 2 weeks. Improved tolerance to pacing and improved lactate metabolism also have been demonstrated after TENS treatment.

The connection between ischemia and pain is complex, and it is not known how neurostimulation influences this. One of the several possibilities is that TENS may increase coronary blood flow, thus reducing ischemia. Certainly, it has been shown that epidural neurostimulation improves microvascular blood flow in peripheral vascular disease.\(^4\)\(^-\)\(^7\) The aim of this study was to test the hypothesis that TENS treatment may relieve the ischemia of angina by increasing coronary blood flow.

Methods

Patients

Group 1. This group comprised 34 patients with typical symptoms of angina and completely normal coronary arteries on angiography as reviewed by two independent observers. All the patients had continued to remain symptomatic despite reassurance after their initial cardiac catheterization. The duration of symptoms was greater than 6 months in all patients. None of the patients had hypertension, diabetes mellitus, lung disease, or valvular heart disease. All patients had stable symptoms of angina for the previous 2 months. There was no evidence of coronary spasm or myocardial bridging in these patients.

Group 2. This group comprised 15 patients who had documented significant coronary artery disease on angiography affecting the right coronary artery. Significant coronary artery disease was defined as >50% reduction in intraluminal diameter of the right coronary artery. The left coronary artery was normal in all patients. These patients were selected so that coronary flow velocity measurements could be undertaken by a Judkins-type Doppler catheter in the normal left coronary system in the absence of any stenoses that may affect measurements. One patient had previous cardiac surgery for an atrial septal defect and had developed angina subsequently. The duration of symptoms was >6 months in all patients, and symptoms of angina had been stable for the previous 2 months. None of the patients had hypertension, diabetes mellitus, lung disease, or valvular heart disease.

Group 3. This group comprised 16 patients with heart transplants and completely normal coronary arteries on angiography. None of these patients had chest pain. These patients were undergoing their routine follow-up cardiac catheterization. Coronary occlusive disease is the main cause of morbidity and mortality more than 1 year after orthotopic cardiac transplantation.\(^12\) Clinical monitoring for the detection of coronary occlusive disease is dependent on serial coronary angiography. Currently, we follow our transplant patients annually with repeat coronary angiography; the patients studied were recruited over a period of 3 months. The duration after transplantation of the patients studied was variable and was determined by the patients scheduled for repeat coronary angiography and giving consent for the study during this period. The minimum duration after transplantation was 12 months and the maximum 100 months. None of the patients

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had hypertension, diabetes mellitus, lung disease, or valvular heart disease. All patients were receiving cyclosporine and azathioprine immunosuppression with or without steroid treatment (Table 1).

**Echocardiography**

Echocardiographic assessment was performed in all patients. Cross-sectional and M-mode assessment of the left ventricular posterior wall and septal thickness was made in all patients. Patients with a diastolic septal or posterior wall thickness of >11 mm were excluded from the study to minimize any effect of left ventricular hypertrophy on coronary flow measurements. Patients with evidence of mitral or aortic valve disease were also excluded.

**Electric Nerve Stimulator and Technique**

A commercially available transcutaneous nerve stimulator (Compact TENS, Neurotech Ltd, Aylesbury, England) was used in the study. This has two electric channels that are electrically isolated. Each channel is capable of a current output of 0 to 60 mA into 1 kΩ. The two channels can be used and controlled separately. The stimulator allows modulation and adjustment of both pulse width and pulse rate. The pulse width is adjustable from 30 to 300 μs. The pulse rate is adjustable from 1 to 200 Hz. The stimulator has a 9-V alkaline battery as its power source. For our study, the stimulator was set to deliver constant-current pulses of 300 milliseconds. The pulse repetition frequency was kept at 150 Hz. The intensity of the stimulation was individually adapted to a level immediately below that producing pain (10 to 60 mA).

For the study, electrode paste was applied to the contact surface to lower the skin impedance. Electrodes (50×35 mm) were placed 10 to 30 cm apart on the chest of the patient at the usual site of their most intense pain (groups 1 and 2). The interelectrode distance was 20 cm in all patients except for 2 patients (10 cm) in group 1 in whom the electrode position was altered because of difficulties with electrode application onto the chest wall and 1 patient (30 cm) in group 2 in whom the electrodes were placed to avoid lesions of psoriasis. In the transplant group (group 3), the electrodes were placed 20 cm apart on the anterior chest wall over the precordium. The electrodes were connected to the stimulator, and the stimulation was adjusted to a level immediately below that producing pain. The level of stimulation was noted, and the stimulator then was turned off. Cardiac catheterization was then performed, and baseline measurements were recorded. The TENS treatment then was given for 5 minutes, and the measurements were repeated immediately after.

**Table 1. Patient Variables**

<table>
<thead>
<tr>
<th>Group 1 (n=34)</th>
<th>Group 2 (n=15)</th>
<th>Group 3 (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55±9</td>
<td>57±10</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.3±12.3</td>
<td>77.4±11</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.7±1.3</td>
<td>12.9±1.1</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>14±10</td>
<td>9±6</td>
</tr>
<tr>
<td>Urea, mmol/L</td>
<td>5.6±0.98</td>
<td>6.2±0.9</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.6±0.8</td>
<td>5.4±0.6</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>101±14</td>
<td>111±12</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>6.38±0.83</td>
<td>6.4±0.8</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>10.5±4.0</td>
<td>11±3</td>
</tr>
<tr>
<td>Median time after operation, mo</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**Antianginal drugs**

| Nitrates      | 18            | 15            | 0             |
| Calcium antagonists | 23            | 12            | 0             |
| β-Blockers    | 19            | 6             | 0             |
| Azathioprine  | 0             | 0             | 16            |
| Cyclosporine  | 0             | 0             | 16            |
| Steroids      | 0             | 0             | 6             |

ESR indicates erythrocyte sedimentation rate; LVEDP, left ventricular end-diastolic pressure. Values are expressed as mean±SD where appropriate.

**Cardiac Catheterization Study**

The patients were fasted overnight before cardiac catheterization. All vasoactive cardiac medications were stopped for at least 48 hours. Coronary angiography was performed by the Judkins technique using the right femoral approach in all patients. Coronary injections were performed manually with up to 8 mL of intracoronary radiopaque contrast (Urografin or Niopam), and cinefilm recordings were made in multiple projections. To eliminate any vasoactive effects of the contrast medium, at least 10 minutes were allowed to lapse before coronary blood flow velocity measurements were recorded.

A Judkins-type 8F Doppler-tipped coronary catheter (Cor- dis Corp, Miami, Fla) was advanced to the ascending aorta over a 0.035-in. J-tipped guide wire and then positioned at the left coronary ostium. This catheter has been validated before for measurements of coronary flow velocity and coronary flow reserve, and the technique is described in detail elsewhere.13,14 The catheter was then flushed and filled with saline. Velocity signal generation and processing was achieved with a standard.
### Table 2. Systemic Hemodynamics and Coronary Blood Flow Velocity Measurements

<table>
<thead>
<tr>
<th></th>
<th>Resting Data</th>
<th>After TENS Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1 (n=34)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats per minute</td>
<td>69±16</td>
<td>69±17</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>130±21</td>
<td>132±25</td>
</tr>
<tr>
<td>CBFV, cm/s</td>
<td>6.8±4.1</td>
<td>10.5±5.7*</td>
</tr>
<tr>
<td>RPP</td>
<td>8919±2352</td>
<td>8974±2760</td>
</tr>
<tr>
<td><strong>Group 2 (n=15)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats per minute</td>
<td>72±15</td>
<td>73±15</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>135±18</td>
<td>133±16</td>
</tr>
<tr>
<td>CBFV, cm/s</td>
<td>6.4±2.5</td>
<td>11.3±6.7*</td>
</tr>
<tr>
<td>RPP</td>
<td>9627±2162</td>
<td>9694±2214</td>
</tr>
<tr>
<td><strong>Group 3 (n=16)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats per minute</td>
<td>91±9</td>
<td>90±11</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>142±21</td>
<td>140±20</td>
</tr>
<tr>
<td>CBFV, cm/s</td>
<td>7.7±4.1</td>
<td>7.5±4.1</td>
</tr>
<tr>
<td>RPP</td>
<td>12 807±2061</td>
<td>12 656±2307</td>
</tr>
</tbody>
</table>

TENS indicates transcutaneous electrical nerve stimulation; HR, heart rate; BP, blood pressure; CBFV, coronary blood flow velocity; and RPP, rate-pressure product. Values are given as mean±SD.

*P<.001.

velocimeter (model MDV-20, Millar Instruments, Houston, Tex). The velocimeter was range-gated and calibrated with an arbitrary internally set calibration of 0 to 100 cm/s (1 kHz=3.75 cm/s) for full-scale deflection (0 to 10 cm on the recorder). The Judkins Doppler was connected to the Millar velocimeter, and the catheter position was adjusted to obtain a stable position with good quality phasic and mean coronary blood flow velocity signals. Injection of contrast through the Doppler catheter lumen fully opacified the coronary artery and identified the relative catheter-artery position. The left coronary system was centered for optimal viewing, and the angiograms were reviewed to select the best two views for repeating the angiogram after the period of TENS.

Resting coronary blood flow velocity, heart rate, and mean arterial and systolic blood pressures were recorded on a Mingograf recorder (Siemens-Elema, Sweden). The transcutaneous nerve stimulator was then turned on for 5 minutes, and the measurements were repeated immediately after the treatment period. The coronary angiograms were repeated in the preselected views immediately after recording the above data.

**Quantitative Measurements**

Quantitative measurements of the coronary artery diameters were performed using digital electronic calipers (Sandhill Scientific Inc). This method has been used previously to assess the arterial diameter of coronary vessels and is reproducible with minimal interobserver and intraobserver variation.13-17 The digital caliper is an application of the concept first described by Gensini et al.14 The device has a variability (standard deviation of multiple estimates) approximating ±6% on estimates of "percent stenosis" and ±0.18 mm on estimates of minimal lumen diameter.19 The mean error of the caliper estimates is not different from zero.20 It has been shown previously in animal experiments that resting coronary flow is not affected until the coronary arterial diameter is reduced by 85%, and the capacity to increase flow over resting basal levels in response to a vasodilatory stimulus does not disappear until constriction of the arterial diameter of >85%.20 Studies in humans have suggested that a 50% to 70% reduction in coronary diameter is necessary before coronary blood flow reserve is affected.21 The digital caliper provides adequate resolution and accuracy to detect any significant changes in coronary arterial diameter that may lead to changes in coronary blood flow.

Two selected views were taken and projected by a Tagarno system onto a sheet of paper. The arterial diameters of the left anterior descending coronary artery and the circumflex artery were measured from tracings of the projected images in diastole, at a distance of 3 cm from the tip of the Doppler catheter. The diameter for each artery was calculated as the mean of the measurements of the two views. The measurements were performed by two independent observers so that interobserver and intraobserver variation could also be calculated.

**Reproducibility**

To assess the reproducibility of the effects of TENS, we repeated the study in 10 chest pain patients (group 1), 10 coronary artery disease patients (group 2) in whom there was at least a 25% increase in the resting coronary blood flow velocity, and in 10 transplant patients (group 3). In all patients, the coronary flow velocity was allowed to return to the original resting level after the initial TENS treatment before continuing with this part of the study. In addition, in these patients we also measured epinephrine and norepinephrine levels in the aortic root before and after the application of TENS.

**Catecholamine Measurements**

The effects of neurostimulation have been likened to those of sympathectomy, and it has been suggested previously that neurostimulation may inhibit sympathetic outflow.10 To study the effect of TENS on serum catecholamine levels in our study, blood samples were taken from the aortic root before and after
the application of TENS. Epinephrine and norepinephrine levels were determined by a high-performance liquid chromatography technique.\textsuperscript{22}

**Statistical Methods**

Values are reported as mean±SD. All comparisons were performed using the Wilcoxon matched pairs test. A value of $P<.05$ was considered to be statistically significant.

**Ethical Approval**

The study was approved by the Huntingdon District Health Authority Ethical Committee, and full informed consent was obtained from all patients before the study.

**Results**

Table 1 shows relevant patient information, blood results, and drug treatment details. Of the transplanted patients, 10 originally underwent transplantation for ischemic heart disease. The remaining 6 patients were transplanted for dilated cardiomyopathy.

**Systemic Hemodynamic Effects**

In all three groups there were no significant systemic hemodynamic changes induced by TENS treatment. There were no significant differences in heart rate, systolic blood pressure, or mean arterial pressure. As a result, there was no significant difference in the rate-pressure product (see Table 2).

**Coronary Blood Flow Velocity Changes**

There was a significant increase in the resting coronary flow velocity in group 1 patients (6.8±4.1 to 10.5±5.7 cm/s, Fig 1) and group 2 patients (6.4±2.5 to 11.3±6.7 cm/s, Fig 2) after TENS treatment. However, TENS treatment did not increase the resting coronary flow velocity in group 3 (7.7±4.1 versus 7.5±4.1 cm/s, Fig 3). There was no difference in the resting coronary flow velocity or in the response to TENS between men and women in groups 1 and 2 (see Tables 2 and 3).

**Coronary Artery Diameter Measurements**

Arterial diameter measurements were reproduced with minimal interobserver ($r=.90$) and intraobserver variation ($r=.91$). There was no significant difference in the arterial diameters of the left coronary system as a result of TENS in all three groups (Table 4).

**Reproducibility**

There was again a significant increase in the coronary blood flow velocity in group 1 and group 2 patients but not in group 3 patients after the application of TENS. Once again, there were no significant hemodynamic changes induced by TENS (Table 5).

**Catecholamine Measurements**

In group 1 patients, there was a significant decrease in the arterial epinephrine concentration ($P=.01$) after TENS application. However, there was no significant difference in the norepinephrine levels. Similarly, there was a significant decrease in the arterial epinephrine concentration ($P=.01$) in group 2, and there was no significant difference in the norepinephrine levels. In group 3 patients, both the epinephrine and norepinephrine levels showed no significant change after TENS application.

**Discussion**

Coronary flow measurements are being used increasingly in clinical cardiology. Until recently, inaccuracies
had limited the methods of assessing coronary blood flow. The use of small-diameter intracoronary Doppler flow catheters has now allowed subselective estimations of coronary blood flow velocity in individual coronary vessels and has become the most extensively used and validated method in the measurement of coronary flow velocity. However, the major limitation of this technique is that instrumentation of the coronary artery is required with the potential of serious complications such as coronary dissection, vasospasm, and thrombosis. Also, the very nature of their use in individual coronary vessels means that only the response of one coronary vessel may be studied at any one time. For assessment of the left coronary circulation, we used the Judkins-type Doppler catheter in our study. These catheters have been validated previously and have been shown to offer a safe, simple, and accurate alternative to the conventional intracoronary Doppler catheters.\textsuperscript{13,14} The use of Judkins Doppler catheters also allowed us to examine the physiological and pharmacological responses of the entire left coronary system, which supplies the left ventricle. If TENS treatment does influence coronary blood flow, these catheters would therefore be more suited to assess the coronary circulation. Since we chose to study patients with angiographically normal left coronary arteries, the subselective intracoronary measure-
ments that would have been required in vessels with significant coronary artery disease were not necessary.

The aim of our study was to investigate whether TENS can influence coronary blood flow. Our study has shown that TENS can increase coronary blood flow velocity significantly in the chest pain group of patients (groups 1 and 2), although it had no significant effect on the transplant patients (group 3). The effect of TENS on the coronary blood flow velocity in these patients was highly reproducible. Moreover, TENS did not significantly affect systemic hemodynamics. The level of arterial epinephrine decreased significantly after TENS treatment in the chest pain patients (groups 1 and 2), although the level of norepinephrine was unchanged. The arterial catecholamine levels were unchanged in the transplant group (group 3).

How does neurostimulation work? The understanding of the effects of neurostimulation in patients with pain is based on the theory of segmental pain inhibition postulated by Melzack and Wall. Their gate control theory states that inhibition of the flow of pain impulses occurs at the first synaptic station in the spinal cord by means of a presynaptic neuron system. They assumed that this system was fed by collateral nerves from both large afferent A fibers, which do not transmit pain, and small myelinated and unmyelinated C fibers. The C fibers inhibit the system and thus prepare the way for increased transmission (the gate was opened), whereas activity in A fibers excited the system and thus resulted in suppression of the transmission to the next neuron chain (the gate was closed). This theory gives a crude explanation for the variability of pain sensation. High-frequency electrical stimulation with pulse widths of between 100 and 200 milliseconds, which stimulates the large A fibers but not the C fibers, reduced the sensation of pain. There is additional evidence that TENS may act by releasing endorphins and inhibiting transmission of noxious stimuli on various levels. TENS may exert its pain-reducing effect on anginal pain by activating enkephalinergic systems either at segmental levels in the spinal cord or possibly locally in the heart.

The effects of neurostimulation have been likened to sympathectomy. Although the relief of the pain of angina alone may indirectly reduce ischemia by reducing reflex sympathetic nervous activity, stimulation of the dorsal column may have a direct effect. Stimulation of the dorsal column may lead to a spread of currents into the intermediate columns of the gray area, releasing segmental spinal reflexes that tonically inhibit sympathetic discharge, and this may cause vasodilatation. It has been shown that prostaglandins also may play a role in mediating the increase in skeletal muscle blood flow caused by activity in the afferent fibers. A similar mechanism may be active in the heart. It is postulated that TENS may produce its analgesic effects by inhibiting sympathetic outflow by influencing the connection between pain fibers and sympathetic neurons in the dorsal horn of the spinal cord as a result of activation of segmental reflexes.

Previous studies have shown that treatment with TENS in patients with angina reduces pain, increases tolerance to pacing, improves myocardial lactate metabolism, and is associated with less pronounced ST segment depression. In long-term studies, the group treated with TENS demonstrated an increased work capacity as assessed by repeated bicycle ergometry tests, had reduced frequency of angina attacks, and had a reduced consumption of nitrates. It has been suggested that this beneficial effect of TENS is due to an antiangiinal as well as an anti-ischemic effect. One mechanism of action suggested in these studies has been that there may be left ventricular afterload reduction caused by arteriolar dilatation, indicated by a drop in systemic vascular resistance and systolic blood pressure and a rise in cardiac index leading to a decrease in myocardial oxygen demand. That these effects may be associated with decreased sympathetic activity was thought to be indicated by a drop in arterial concentration of norepinephrine and epinephrine in patients in whom angina disappeared during treatment at corresponding pacing rates.

TENS has been shown to cause a significant decrease in the blood pressure of hypertensive rats. In humans, TENS treatment to control the pain of parturition has been shown to increase placental blood flow. TENS also causes vasodilatation in patients with peripheral

### Table 4. Coronary Artery Diameter Measurements

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting Cx diameter, mm</td>
<td>4.1±0.9</td>
<td>4.0±1.0</td>
<td>4.3±1.2</td>
</tr>
<tr>
<td>After TENS</td>
<td>4.0±1.0</td>
<td>4.0±1.0</td>
<td>4.4±1.1</td>
</tr>
<tr>
<td>Resting LAD diameter, mm</td>
<td>4.2±0.7</td>
<td>3.9±1.1</td>
<td>4.4±0.7</td>
</tr>
<tr>
<td>After TENS</td>
<td>4.3±0.6</td>
<td>3.9±1.1</td>
<td>4.3±0.5</td>
</tr>
</tbody>
</table>

Cx indicates circumflex coronary artery; TENS, transcutaneous electrical nerve stimulation; and LAD, left anterior descending coronary artery. Values are given as mean±SD.

### Table 5. Reproducibility of the Effects of TENS

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=10)</th>
<th>Group 2 (n=10)</th>
<th>Group 3 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Study</td>
<td>Second Study</td>
<td>First Study</td>
</tr>
<tr>
<td>Pre-TENS HR, bpm</td>
<td>64±8</td>
<td>64±8</td>
<td>68±9</td>
</tr>
<tr>
<td>Post-TENS HR, bpm</td>
<td>63±10</td>
<td>64±10</td>
<td>68±10</td>
</tr>
<tr>
<td>Pre-TENS MAP, mm Hg</td>
<td>94±12</td>
<td>95±11</td>
<td>96±11</td>
</tr>
<tr>
<td>Post-TENS MAP, mm Hg</td>
<td>96±12</td>
<td>95±12</td>
<td>96±12</td>
</tr>
<tr>
<td>Pre-TENS CBFV, cm/s</td>
<td>6.0±1.8</td>
<td>6.3±1.5</td>
<td>6.5±1.8</td>
</tr>
<tr>
<td>Post-TENS CBFV, cm/s</td>
<td>13.7±5.5</td>
<td>13.8±5.5</td>
<td>13.7±5.2</td>
</tr>
</tbody>
</table>

TENS indicates transcutaneous electrical nerve stimulation; HR, heart rate; bpm, beats per minute; MAP, mean arterial pressure; and CBFV, coronary blood flow velocity. Values are given as mean±SD.
arterial disease. Recently, Kaada et al.\(^3\) have shown that TENS can cause a significant lowering of mean femoral arterial pressure and systemic vascular resistance. This effect was considered to be due to an increase in peripheral microcirculation as a result of inhibition of the sympathetic system.

Does neurostimulation increase coronary blood flow? Noninvasive studies have suggested that there is less ischemia in some patients.\(^8\)-\(^11\)\(^,\)\(^23\) However, other studies have shown that although there was a reduction in angina, an increase in the time to onset of ischemia, and a higher perfusion at rest during stimulation than in controls, there was no significant increase of perfusion to abnormal segments after maximal exercise as assessed by positron emission tomography.\(^3\)\(^4\) It has been suggested that any changes in the perfusion caused by neurostimulation are small, occur mainly in the ischemic areas, and will be difficult to detect in the heart. It may be that neurostimulation can result in the adjustment of local flow without any increase in total flow, for example, the so-called “Robin Hood effect” of aminophylline.\(^3\)\(^5\) However, our study has demonstrated that TENS can increase the resting coronary flow velocity, and this may support the findings of Landsheere et al.,\(^3\)\(^4\) who reported an increased perfusion during stimulation than in controls.

Similar to most other previous studies, our study does not demonstrate any effect of TENS at rest on systemic hemodynamics.\(^8\)-\(^10\) In the study reported by Kaada et al.,\(^3\)\(^2\) which showed that TENS application can significantly lower mean femoral arterial pressure, the duration of TENS treatment was 20 minutes, and low-frequency electrical nerve stimulation (2 Hz) was used. In our study, high-frequency (150 Hz) electrical nerve stimulation was used, and the duration of stimulation was only 5 minutes. It has been claimed previously that high-frequency electroacupuncture (100 Hz) causes mainly segmental analgesia, whereas the effects of low-frequency stimulation (<10 Hz) are more generalized in both humans and animals.\(^3\)\(^6\) It may be that high-frequency TENS given for the short duration in our study did have a predominantly segmental effect, and this may explain the lack of any effect on the mean arterial pressure. If the duration had been prolonged, then we may have seen a systemic effect.

One possible mechanism by which TENS treatment may influence coronary blood flow may be by affecting the coronary vascular tone as a result of changes in the neural tone. We studied the transplant group because the heart in these patients is denervated and they provide an in vivo model of a denervated heart. It is interesting to note that TENS treatment did not affect the resting coronary blood flow velocity in the transplant group, although there was a significant increase in the chest pain groups. This would also suggest that the mechanism by which TENS may affect coronary blood flow may have an underlying neural basis.

There was necessarily a substantial variability associated with physical application of the electrical stimulation dependent on patient tolerance to the stimulation and the positioning of the electrodes over the painful areas. However, the technique used is similar to other reported studies.\(^8\)-\(^11\) The interelectrode distance was the same (20 cm) in most patients and is unlikely to have influenced the difference seen in the response to TENS. Also, in each case, the patient acted as their own control. It may be argued that there was no effect seen in the transplant group because of their previous surgery and the resulting sternotomy scars, which may have resulted in differences in sensitivity to TENS and pain perception or a failure of TENS transmission. In all our transplant patients, the electrodes were placed well clear of the sternotomy scar on either side of the midline. In the only patient with a previous sternotomy scar from cardiac surgery in our study (patient 11, group 2, Table 3), there was a significant increase in coronary flow velocity in response to TENS, which suggests that sternotomy scars do not lead to failure of TENS transmission. Indeed, one would not expect sternotomy scars to interfere with TENS transmission on anatomic grounds because the innervation of the anterior chest wall is symmetrically segmental. Furthermore, TENS treatment has been shown to be effective in relieving pain after thoracotomy and to reduce the incidence of lung atelectases.\(^3\)\(^7\)

The heart rate, systolic blood pressure, and the rate-pressure product were higher in group 3. It has been shown in heart transplant patients that increases in heart rate produce an increase in resting coronary flow velocity without a proportionate increase in the hyperemic coronary flow velocity.\(^3\)\(^8\) Consequently, coronary flow reserve measurements decrease with increasing heart rate. However, there is little reduction in the hyperemic coronary flow velocity in absolute terms with increasing heart rates of up to 120 beats per minute.\(^3\)\(^8\) A similar study in patients undergoing elective coronary angiography for the evaluation of chest pain has demonstrated that sudden increases in heart rate but not mean arterial pressure lead to a substantial reduction in maximal coronary flow reserve—from 3.7±0.9 at the heart rate of 71±18 beats per minute at rest to 2.6±0.5 during pacing at 120 beats per minute.\(^3\)\(^9\) It is therefore possible that the higher resting heart rate in the transplant group may have resulted in the failure of the transplant patients to respond to TENS. However, it is of note that even at the heart rate of 120 beats per minute in Rossen and Winniford’s study,\(^3\)\(^9\) there was still a mean increase in coronary flow velocity by 2.6-fold from the resting values, indicating that the ability of the coronary microcirculation to increase coronary blood flow toward hyperemia is still preserved although it may be impaired. It would not be unreason-

### Table 6. Catecholamine Levels

<table>
<thead>
<tr>
<th>Group (n=10)</th>
<th>Before TENS</th>
<th>After TENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine, ng/L</td>
<td>89.3±25.9</td>
<td>60.6±18.4*</td>
</tr>
<tr>
<td>Norepinephrine, ng/L</td>
<td>300±146.2</td>
<td>284.5±144.5</td>
</tr>
<tr>
<td>Group 2 (n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine, ng/L</td>
<td>102.2±27.2</td>
<td>64.1±19.1*</td>
</tr>
<tr>
<td>Norepinephrine, ng/L</td>
<td>341.8±158.8</td>
<td>334.6±157.6</td>
</tr>
<tr>
<td>Group 3 (n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine, ng/L</td>
<td>68.7±32.2</td>
<td>67.6±32.1</td>
</tr>
<tr>
<td>Norepinephrine, ng/L</td>
<td>338.3±95.2</td>
<td>332±94.1</td>
</tr>
</tbody>
</table>

TENS indicates transcutaneous electrical nerve stimulation.

*P<.05. Values are given as mean±SD.
able to assume that the higher resting heart rate (94±11 beats per minute) in the transplant group compared with the other groups in our study would not lead to a total lack of response to TENS because the increased heart rate would not completely abolish the ability of the coronary circulation to increase coronary flow, although this possibility cannot be entirely excluded. Increases in arterial pressure increase both the resting and hyperemic coronary flow velocities.³⁸ Consequently, the coronary flow reserve remains unaffected. We would not expect the increased systolic pressures to affect the ability of the coronary circulation in transplant patients to respond to TENS.

The increase in coronary flow velocity in the chest pain groups, in the absence of a significant difference in arterial pressure and heart rate, may have resulted from a change in the coronary artery diameter. However, the quantitative measurements of the artery diameters before and after TENS have shown that there was no significant change in the vessel diameters. If TENS does indeed affect the coronary circulation, then the possible mechanisms of its actions are not clear. It may either alter the neural tone of the coronary microvasculature without affecting the large epicardial vessels, thus resulting in increased blood flow, or may produce a similar effect by causing the local release of substances that are able to affect the microcirculation. There has been some interest previously in the search for the mediators of vasodilation peripherally produced by TENS, but no active vasodilator has been identified in the heart.³²

There was variability in the response to TENS in groups 1 and 2 that was independent of threshold stimulation and the site of electrode placement. This may suggest individual differences in sensitivity to neurostimulation and underlines the complex mechanisms that may be responsible for the effects of TENS.

The results of the catecholamine measurements are in keeping with previous studies and suggest sympathoinhibition.¹⁰,³² Emanuelsson et al¹⁰ suggested that the reduction in the sympathetic activity during TENS was mainly secondary to pain relief rather than a direct influence on the sympathetic system. However, there is other evidence supporting the theory that, in addition to its pain-relieving effect, TENS may influence autonomic systems by suppressing sympathetic overactivity.³¹ Our study also supports this because none of the patients during the study experienced any chest pain, and the reduction in arterial epinephrine level occurred as a result of the effect of TENS at rest in the absence of any ischemia.

Study Limitations

Our study was open and therefore was exposed to bias. It is almost impossible to design a blind study of treatment with TENS because there is no placebo equivalent for the sensation of transcutaneous neurostimulation. However, in our study, the patients acted as their own control, and the results of the reproducibility study demonstrated consistent responses in the chest pain and transplant patients.

Evidence now exists for spontaneous reinnervation of the transplanted heart and restoration of sinus arrhythmia and baroreceptor function.⁴⁰ None of the transplant patients studied demonstrated sinus arrhythmia on ECG recordings. However, it has been shown recently that the response of the sinus node to stimulatory maneuvers cannot be taken as evidence for or lack of reinnervation of the remainder of the heart because reinnervation after cardiac transplantation is regionally heterogeneous.⁴¹ We did not perform tyramine studies in the transplant patients for the presence of reinnervation, which may have helped us to partition the attenuated response of these patients to a peripheral sensor reception problem or a central effect.

All the transplant patients were on immunosuppression therapy, which was continued. It is possible that these drugs may have affected pain threshold and coronary vasoreactivity. However, we are not aware of any evidence to suggest this possibility. Coronary microvascular vasodilatory responses after cardiac transplantation do not seem to be affected by cyclosporine.⁴²

Conclusions

TENS can reproducibly increase resting coronary blood flow velocity. The lack of any effect in the transplant patients suggests that the effect of TENS may be mediated by neural mechanisms. The lack of any changes in the large epicardial coronary artery diameter suggests that the site of vascular action is at the microcirculatory level. These may vasodilate, causing an increase in coronary blood flow as a result of a local production of vasodilatory substances or directly by a reduction in sympathetic activity or both. Our study does suggest a decreased sympathetic activity locally in the heart, although any accompanying production of vasodilator substances cannot be ruled out.

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