Sympathetic ganglion transcutaneous electrical nerve stimulation after coronary artery bypass graft surgery improves femoral blood flow and exercise tolerance

Gerson Cipriano, Jr.,1 J. Alberto Neder,2 Daniel Umpierre,3 Ross Arena,4 Paulo J. C. Vieira,3 Adriana M. Güntzel Chiappa,5 Jorge P. Ribeiro,31 and Gaspar R. Chiappa1,6

1Physical Therapy Department, University of Brasilia, Brasilia, Brazil; 2Laboratory of Clinical Exercise Physiology, Division of Respiratory and Critical Care Medicine, Kingston General Hospital, Queen’s University, Kingston, Ontario, Canada; 3Exercise Pathophysiology Research Laboratory and Cardiology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; 4Department of Physical Therapy, College of Applied Health Sciences, University of Illinois Chicago, Chicago, Illinois; 5Intensive Care Unit, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; and 6Public Health Research Group, Division of Physical Therapy, Serra Gaucha College, Caxias do Sul, Brazil

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Cipriano G Jr., Neder JA, Umpierre D, Arena R, Vieira PJ, Chiappa AM, Ribeiro JP, Chiappa GR. Sympathetic ganglion transcutaneous electrical nerve stimulation after coronary artery bypass graft surgery improves femoral blood flow and exercise tolerance. J Appl Physiol 117: 633–638, 2014. First published August 7, 2014; doi:10.1152/japplphysiol.00993.2013.—We tested the hypothesis that transcutaneous electrical nerve stimulation (TENS) over the stellate ganglion region would reduce sympathetic overstimulation and improve femoral blood flow (FBF) after coronary artery bypass graft surgery. Thirty-eight patients (20 men, 24 New York Heart Association class III-IV) were randomized to 5-day postoperative TENS (n = 20; 4 times/day; 30 min/session) or sham TENS (n = 18) applied to the posterior cervical region (C7-T4). Sympathetic nervous system was stimulated by the cold pressor test, with FBF being measured by ultrasound Doppler. Femoral vascular conductance (FVC) was calculated as FBF/mean arterial pressure (MAP). Six-min walking distance established patients’ functional capacity. Before and after the intervention periods, pain scores, opiate requirements, and circulating β-endorphin levels were determined. As expected, preoperative MAP increased and FBF and FVC decreased during the cold pressor test. Sham TENS had no significant effect on these variables (P > 0.05). In contrast, MAP decreased in the TENS group (125 ± 12 vs. 112 ± 10 mmHg). This finding, in association with a consistent increase in FBF (95 ± 5 vs. 145 ± 14 ml/min), led to significant improvements in FVC (P < 0.01). Moreover, 6-min walking distance improved only with TENS (postsurgery-presurgery = 35 ± 12 vs. 6 ± 10 m; P < 0.01). TENS was associated with lesser postoperative pain and opiate requirements but greater circulating β-endorphin levels (P < 0.05). In conclusion, stellate ganglion TENS after coronary artery bypass graft surgery positively impacted on limb blood flow during a sympathetic stimulation maneuver, a beneficial effect associated with improved clinical and functional outcomes.

IT IS WELL ESTABLISHED THAT moderate-to-severe coronary artery disease (CAD), particularly when symptomatic, is associated with sympathetic overactivation [as recently reviewed by Rosen (33)]. Sympathetically mediated vasoconstriction and paroxysmal tachycardia then increase systemic arterial blood pressure and myocardial O2 consumption, further compromising myocardial O2 supply/demand balance (13, 41). Peripheral vasoconstriction can also reduce muscle blood flow, in either inactive beds or those perfusing contracting muscle groups (10, 34). Most patients with extensive CAD require coronary artery bypass graft (CABG) surgery, which is expected to further increase sympathetic activation and its deleterious consequences (3, 40). The resulting impairment in muscle O2 delivery, therefore, might contribute to worsen postoperative exercise tolerance in CAD patients who underwent CABG surgery (44, 48).

Considerable effort has been made to establish clinically feasible interventions to restore autonomic imbalance and functional exercise capacity in this patient population (3, 43, 44, 48). Transcutaneous electrical nerve stimulation (TENS) emerges as a potentially useful strategy to decrease angina severity (5, 9, 27–29) and improve local blood flow (2, 18, 35). Of note, these phenomena might be mediated by myocardial release of β-endorphin (9) and lower sympathetic activation (10, 36). There is some intriguing evidence, however, that TENS can modulate sympathetic output at a more systemic level (6, 16, 36). In fact, we recently described that TENS over the stellate (sympathetic) ganglion region increased lower limbs blood flow and attenuated cardiac sympathetic activity (estimated by heart rate variability) in volunteers with normal baseline sympathetic tonus (46). Considering that TENS is particularly beneficial in diminishing sympathetic overstimulation when the adrenergic tonus is upregulated, (16, 36), we raised the hypothesis that TENS would be effective in attenuating sympathetic-induced vasoconstriction in CAD patients submitted to CABG surgery. We also reasoned that these effects would add to TENS analgesic properties (11, 12, 14, 26, 37, 42) and contribute to restoration of patients’ postoperative functional capacity.

The present study, therefore, is the first to investigate the potential role of stellate ganglion TENS to lessen sympathetically mediated vasoconstriction within the lower limbs after CABG surgery in CAD patients. We also hypothesized that, in addition to its well-known analgesic and opiate-sparing effects (11, 12, 14, 26, 37, 42), TENS would be associated with improved postoperative exercise tolerance compared with sham TENS.
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METHODS

Study Population

This trial was carried out in patients who were referred for a first-time CABG intervention due to CAD in a tertiary center. The following criteria were used for surgery referral: 1) patients with unstable angina presenting with left coronary lesion or trivessel disease with reduced left ventricular ejection fraction (<50%), or bivessel disease with proximal obstruction of the anterior descending artery and reduced left ventricular ejection fraction, or single- or bivessel disease without proximal obstruction of the anterior descending artery but at high risk according to noninvasive tests, or single-vessel disease with proximal obstruction of the anterior descending artery; and 2) patients with acute myocardial infarction showing evidences of clinical instability and unfavorable anatomy for percutaneous transluminal coronary angioplasty or unsuccessful percutaneous transluminal coronary angioplasty with favorable coronary anatomy. Patients were required to quit smoking before the surgery. Age greater than 75 yr, chronic renal failure (dialysis for more than 3 mo), unstable angina in the 48 h before CABG, moderate or severe valve disease, complex cardiac arrhythmias, recent stroke (6 mo), and/or inability to exercise the lower limbs (orthopedic disease) were excluded. We also excluded subjects with previous restrictive or obstructive pulmonary disease [forced vital capacity <80% predicted and/or forced expiratory volume in 1 s (FEV1)/femoral vascular conductance (FVC) < 0.7], and those with a history of asthma. The protocol was approved by the Institution Committee for Ethics in Research, and all subjects signed an informed consent form. The study received a Clinical Trial Registration Number of NCT01777659.

Study Design

Suitable patients were identified in advance from the institutional outpatient clinic on CAD. The investigators were informed when the patient would be electively admitted for CABG surgery. On admission in the preoperative ward, they were contacted and signed an informed consent. After being told that two different stimulation protocols would be compared, they were randomized (Graphpad StatMate, La Jolla, CA) to TENS or sham electrical stimulation. Patients underwent cold pressor test and 6-min walking tests 24–48 h before the surgery. Post-surgery intervention started as soon as the patients were discharged from the Intensive Care Unit (usually within 24–48 h), provided that they were hemodynamically stable with no central venous access in place. At this point, postoperative clinical outcomes were recorded (pain, opiates dosage, and β-endorphin levels). After 5 days of TENS or sham stimulation, physiological and clinical outcomes were reassessed. Measurements were carried out by examiners blinded for the allocation of intervention. During this timeframe, patients were followed by their own physicians and received routine nursing assistance.

TENS

Patients underwent conventional TENS (Endomed 684 Device, Enraf-Nonius B.V., Rotterdam, the Netherlands, GB 3004) or sham TENS for 5 days (4 times/day; 30 min/session). Adhesive electrodes (MultiStick, Axelgaard Manufacturing, Fallbrook, CA) were applied about 3 cm to the right and left of midline vertebral process at C7 and T4 levels. TENS consisted of continuous flow, symmetrical, and/or forced expiratory volume in 1 s/femoral vascular conductance included. We also excluded subjects with previous restrictive or obstructive pulmonary disease with proximal obstruction of the anterior descending artery but at high risk according to noninvasive tests, or single-vessel disease with proximal obstruction of the anterior descending artery; and 2) patients with acute myocardial infarction showing evidences of clinical instability and unfavorable anatomy for percutaneous transluminal coronary angioplasty or unsuccessful percutaneous transluminal coronary angioplasty with favorable coronary anatomy. Patients were required to quit smoking before the surgery. Age greater than 75 yr, chronic renal failure (dialysis for more than 3 mo), unstable angina in the 48 h before CABG, moderate or severe valve disease, complex cardiac arrhythmias, recent stroke (6 mo), and/or inability to exercise the lower limbs (orthopedic disease) were excluded. We also excluded subjects with previous restrictive or obstructive pulmonary disease [forced vital capacity <80% predicted and/or forced expiratory volume in 1 s (FEV1)/femoral vascular conductance (FVC) < 0.7], and those with a history of asthma. The protocol was approved by the Institution Committee for Ethics in Research, and all subjects signed an informed consent form. The study received a Clinical Trial Registration Number of NCT01777659.

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![Diagram](https://i.imgur.com/5wY5.png)

**Fig. 1.** The consort: flow diagram of patients in the study. TENS, transcutaneous electrical nerve stimulation.

Table 1. Baseline characteristics of coronary artery disease patients submitted to TENS or sham TENS

<table>
<thead>
<tr>
<th></th>
<th>Sham TENS</th>
<th>TENS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>66 ± 3</td>
<td>62 ± 4</td>
<td>0.48</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>9/9</td>
<td>11/9</td>
<td>0.91</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27 ± 2</td>
<td>25 ± 2</td>
<td>0.38</td>
</tr>
<tr>
<td>Systemic hypertension, n</td>
<td>15</td>
<td>14</td>
<td>0.78</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>5</td>
<td>6</td>
<td>0.54</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>54 ± 4</td>
<td>51 ± 7</td>
<td>0.67</td>
</tr>
<tr>
<td>NYHA score (I-II/III-IV)</td>
<td>7/11</td>
<td>7/13</td>
<td>0.89</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>16 (88)</td>
<td>18 (90)</td>
<td>0.78</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>14 (77)</td>
<td>15 (75)</td>
<td>0.81</td>
</tr>
<tr>
<td>Lipid-lowering</td>
<td>12 (66)</td>
<td>14 (70)</td>
<td>0.72</td>
</tr>
<tr>
<td>Aspirin</td>
<td>17 (94)</td>
<td>16 (80)</td>
<td>0.82</td>
</tr>
<tr>
<td>No. of grafts, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction, n</td>
<td>8</td>
<td>11</td>
<td>0.41</td>
</tr>
<tr>
<td>Entubation time, h</td>
<td>6 ± 1.5</td>
<td>7 ± 1</td>
<td>0.81</td>
</tr>
<tr>
<td>Femoral artery diameter, mm</td>
<td>7.8 ± 0.5</td>
<td>7.4 ± 0.6</td>
<td>0.45</td>
</tr>
<tr>
<td>Maximal handgrip, kg</td>
<td>22 ± 4</td>
<td>25 ± 5</td>
<td>0.63</td>
</tr>
<tr>
<td>6-Min walking distance, m</td>
<td>295 ± 58</td>
<td>287 ± 49</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Otherwise indicated values are means ± SD; n, no. of subjects. TENS, transcutaneous electrical nerve stimulation; M, male; F, female; NYHA, New York Heart Association; ACE, angiotensin I-converting enzyme.

Variables were significantly greater in the TENS group at baseline (Fig. 2). Preoperative 6-min walking distance, however, did not differ between the groups (Table 1).

TENS was well tolerated by all patients with no reported side effects. As shown in Fig. 2, sham TENS had no significant effect on MAP, FBF, and FVC (P > 0.05). In contrast, MAP decreased in the TENS group (125 ± 12 vs. 112 ± 10 mmHg; P < 0.05). This finding in association with a consistent increase in FBF (95 ± 5 vs. 145 ± 14 ml/min; P < 0.01) led to significant improvements in FVC (0.85 ± 0.05 ml·min⁻¹·mmHg⁻¹ × 100 vs. 1.21 ± 0.11 ml·min⁻¹·mmHg⁻¹ × 100; P < 0.01). Of note, 6-min walking distance increased significantly with TENS, but not with sham (postsurgery-presurgery variations = 35 ± 12 vs. 6 ± 10 m; P < 0.05).

TENS, but not sham, significantly reduced postoperative pain [presurgery vs. postsurgery (Borg scale unity): 7 ± 2 vs. 1 ± 0.5 and 7 ± 2 vs. 8 ± 3, respectively] and opioid usage (20 ± 9 vs. 5 ± 3 and 25 ± 10 vs. 28 ± 8 mg/day; P < 0.01). This was associated with greater levels of circulating β-endorphin with TENS than sham (478 ± 20 vs. 589 ± 59 and 456 ± 26 vs. 478 ± 27 pg/ml, respectively; P < 0.01).

**DISCUSSION**

This randomized controlled trial demonstrated, for the first time, that a 5-day post-CABG surgery program of TENS applied over the stellate ganglion region blunted the physiological effects of sympathetic stimulation on systemic arterial pressure (hypertension) and lower limb perfusion (vasoconstriction). Moreover, TENS was associated with less postoperative pain, significant reductions in opioid usage, and greater walking capacity than sham stimulation. These results indicate that TENS is a safe and efficacious adjunct therapy to mitigate the deleterious consequences of sympathetic overstimulation.

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which might contribute to restore postoperative functional capacity after CABG surgery.

To test the working hypothesis that, like healthy subjects (46), TENS would reduce the peripheral hemodynamic consequences of sympathetic overstimulation, we carefully selected a clinical population in whom the baseline sympathetic tonus is known to be increased (3, 40, 44, 48). In fact, there is clear evidence that the sympathetic nervous system is overactive in patients with active CAD, a deleterious phenomenon worsened under the stress of exercise (48) and cardiac surgery (40). Other clinical and phenotypical features indicate that our patients were representative of the population that undergoes selective CABG, i.e., middle-aged to older patients, overweight, and presenting with comorbidities (Table 1). Consequently, we are confident that our results are externally valid and applicable to real-world conditions.

Improvement in segmental blood flow by sympathetic nerve outflow modulation has been successfully reached by regional sympathetic blockade, either invasively or noninvasively (e.g., TENS) (4). The stellate ganglion, in particular, can be selectively blocked to temporarily eliminate unilateral sympathetic innervation of the head, neck, and upper extremity (4, 21). In fact, this procedure reduced sympathetic outflow and improve blood flow by up to 50% in patients with peripheral vascular disease (2). Stellate ganglion TENS also successfully enhanced the plethysmographic signal of pulse oximetry in posttrauma patients (3). It is rather remarkable, however, that, in the present study, the physiological consequences of cervical TENS were observed remotely from the anatomic sites of stimulation, i.e., in the conduit arteries of the lower limbs. This drives the logical assumption that the effects of stellate ganglion stimulation were not circumscribed to loco-regional sympathetic blockade.

In this context, it could be hypothesized that the modulating effects of TENS on the opioid systems produced more generalized effects. For instance, high-frequency TENS (80 Hz) (39), as used in the present study, may activate μ- and δ-opioid receptors in the spinal cord (38) and, in particular, in the rostral ventromedial medulla (19). These receptors are associated with release of vasoactive substances such as endorphins, which have dual effects in reducing pain and sympathetically mediated vasoconstriction (15, 23–25). Of note, we did find greater circulating levels of β-endorphin in the TENS group. It should be noted, however, that the current knowledge on the role of peripheral nerve stimulation in modulating central sympathetic neuron activity and cardiovascular reflexes has been largely built on electroacupuncture experiments (23–25, 45), the results of which might not be necessarily applicable to TENS (47). Secondary actions of TENS on spinal muscarinic receptors and/or vagal stimulation cannot be entirely ruled out (20, 31). An isolated negative chronotropic effect of TENS (32), however, seems unlikely, as this would elicit reflex vasocon-
striction (to maintain MAP) rather than increase appendicular blood flow. Functional sympatholysis secondary to blockage of afferent information (34) is also unlikely, as the lower limbs were static during the sympathetic stimulation maneuvers. Additional studies, therefore, are warranted to address the precise mechanism(s) underlying the remote effects of stellate ganglion stimulation found in the present study.

We also confirmed previous reports that TENS can reduce postoperative pain and opioid usage (11, 12, 14, 26, 37, 42). This might have importantly contributed to increase patients’ tolerance to exertion after stimulation. It is also tempting to speculate that the observed effects of TENS on appendicular blood flow contributed to enhance exercise tolerance. TENS has been found effective in improving walking capacity in hemiparetic stroke (30) and peripheral arterial disease patients (2). However, these studies used surface TENS to promote sympathetic postganglionic fibers blockade, not stellate ganglion blockade as in the present study. Our laboratory’s previous study with healthy subjects demonstrated that acute application of TENS over the stellate ganglion region improved muscle blood flow during exercise (46). In the present study, however, lack of measurement of blood flow during exercise precludes a definitive statement on this regard.

The present investigation has some important limitations that can drive the interest for future studies. First, it should be recognized that preoperative FBF was significantly higher in the TENS group (Fig. 2), and we cannot rule out that these patients were (by hazard) more reactive to the cold pressor test. On the other hand, lower baseline FBF values in the sham group would make these patients more prone to improvement due to the regression to the mean effect. Nevertheless, increases in FBF with TENS was substantially greater than the postsurgery-presurgery changes observed in the sham group. Second, we did not evaluate muscle sympathetic nerve activity or catecholamine spillover, which could have provided supportive evidence for TENS-induced reduction in sympathetic hyperactivity. Third, we acknowledge that, by not measuring the effects of CABG per se on the sympathetic tonus (i.e., by repeating the maneuvers after the surgery but before stimulation), we cannot be sure that it did not differ between the groups. However, it would be unethical to submit our patients to the stress of sympathetic stimulation in the early postoperative period. Fourth, stellate ganglion blockade is known to reduce the frequency and severity of postsurgery cardiac arrhythmias, another putative beneficial effect of TENS that remains to be investigated.

In summary, this is the first published evidence that postoperative TENS over the stellate (sympathetic) ganglion can partially counterbalance the negative effects of sympathetic overstimulation on MAP and FBF in CAD patients after CABG surgery. TENS was also associated with significant analgesic effects and greater postsurgery functional exercise capacity. These results, therefore, call for additional randomized trials to investigate the therapeutic role of TENS in other clinical scenarios where increased appendicular blood flow can be clinically useful, e.g., early (phase I) cardiac rehabilitation and exacerbation of concomitant peripheral arterial disease.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


