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

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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. 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 simulated 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.

exercise; sympathetic nervous system; TENS; blood flow; exercise capacity

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 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.
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, 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, 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, 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, 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, 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, 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, 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, complex cardiac arrhythmias, recent stroke (6 mo), and/or inability to exercise the lower limbs (orthopedic disease) were excluded.

Stage 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 to the preoperative ward, they were contacted and signed an informed consent form. 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 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, Emraf-Nomius 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 rectangular biphasic pulses calibrated at a 2-Hz frequency and 200-μs pulse duration (162 Gould Electronics, Instruments Systems). The frequency of stimulation was 80 Hz, and the pulse duration was 150 μs. Stimulation intensity (mA) was set at the maximal level at which subjects did not report pain, and no voluntary contraction was observed (42, 46). Frequency was selected to elicit strong sensations of paresthesia but without pain or muscle contractions. For sham stimulation, time between pulses was modified from 330 ms to 33 s to avoid any analgesic effect (7, 8).

Sympathetic Stimulation Test

Procedure. The cold pressor test consists of immersing patients’ hand or feet in ice water to activate the sympathetic nervous system. In the present study, patients were evaluated in the supine position with the knees being flexed at an angle of ~90°. After a baseline recording of 3 min (control period), the subject immersed one hand in a 3–4°C water bath for a 3-min period (immersion period), followed by a 3-min recovery period. Patients were instructed to pull out their hand from water if pain proved unbearable.

Physiological measurements. Mean arterial pressure (MAP, mmHg) was measured in the nondominant arm using a calibrated oscillometric automatic device (Carescare V100, GE Healthcare). Femoral blood flow (FBF, ml/min) was obtained by ultrasound Doppler (Logiq 7, GE Medical Systems, Milwaukee, WI). The system is equipped with two linear array transducers operating at an imaging frequency of 7–8 MHz, as described previously (46). The common femoral artery of the left leg was insonated distal to the inguinal ligament, 2–3 cm proximal to the bifurcation. The blood velocity profile was obtained using the same transducers with a Doppler frequency of 4.0–5.0 MHz, operated in high-pulsed repetition-frequency mode (2–25 kHz) with a sample volume depth of 1.5–3.5 cm. All blood velocity measurements were obtained with the probe positioned to maintain an insonation angle of ≤60°. Using femoral artery diameter and mean blood velocity (Vmean), FBF was calculated as Vmean × (vessel diameter/2)² × 60 (46). The measurements were saved for offline imaging and waveform analysis. For each ultrasound Doppler segment, Vmean was averaged across the first and last half of the recorded clip (20 s), whereas diameter measurements (1–3 per segment) were evaluated during diastole and the relaxation phase of the duty cycle during exercise. Data during the tests were both analyzed in 1-min segments and averaged across the 3 min of testing. FVC was calculated as (FBF/MAP) × 100 (ml·min⁻¹·mmHg⁻¹ × 100) (22).

Clinical Outcomes

The 6-min walking test was performed according to the American Thoracic Society guidelines to assess patients’ functional capacity (1). Postoperative pain was quantified by a standard 0–10 visual analog scale. Opiate (pethidine HCl, 20 mg, maximum 1 mg·kg⁻¹·day⁻¹) doses required for pain control were also recorded. β-Endorphin levels (pg/ml) were measured by a sandwich enzyme immunoassay kit (Phoenix Pharmaceuticals).

Statistical Analysis

Based on our laboratory’s previous results (46), we estimated that a sample size of 10 subjects in each group would have a power of 90% to detect a 10% difference in FBF, with P < 0.05. Descriptive data are presented as means ± SD. Baseline data were compared by nonpaired t-test or Mann-Whitney tests for continuous variables or Fisher exact test for categorical variables. Two-way ANOVA with repeated measures (followed by the Holm-Sidak test) compared the physiological responses during the cold pressor test pre- and postsurgery in sham and active TENS groups. A type I error < 5% indicated statistical significance (P < 0.05).

RESULTS

During the 18-mo recruitment period, 88 patients were screened. Forty-two patients did not meet the inclusion criteria and nine patients refused participation. Forty-six patients were randomized to either TENS (n = 23) or sham (n = 23). Two patients died intraoperatively, and six patients were excluded due to immediate surgery complications. Therefore, 38 patients completed the study (Fig. 1). Twenty-four patients had normal diastolic function, with the other patients showing mild-to-
moderate relaxing abnormalities (7 in each group). As shown in Table 1, the groups were well matched for baseline demographic, clinical, and surgical characteristics.

As expected, preoperative MAP increased and FBF and FVC decreased during the cold pressor test in both groups (data not shown). However, test-rest changes in FBF and FVC were greater in the TENS group ($P < 0.05$). As a consequence, both 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 ($125 \pm 12$ vs. $112 \pm 10 \text{ mmHg}$; $P < 0.05$). This finding in association with a consistent increase in FBF ($95 \pm 5$ vs. $145 \pm 14 \text{ ml/min}$; $P < 0.01$) led to significant improvements in FVC ($0.85 \pm 0.05 \text{ ml/min}\cdot\text{mmHg}^{-1} \times 100$ vs. $1.21 \pm 0.11 \text{ ml/min}\cdot\text{mmHg}^{-1} \times 100$; $P < 0.01$). Of note, 6-min walking distance increased significantly with TENS, but not with sham (post-surgery-presurgery variations $= 35 \pm 12$ vs. $6 \pm 10 \text{ m}$; $P < 0.05$).

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

Fig. 2. Pre- and postcoronary artery bypass graft surgery mean arterial pressure (MAP), femoral blood flow (FBF), and femoral vascular conductance (FVC) during the cold pressor test in patients submitted to sham TENS (n = 20) and active TENS (n = 18). Pre, presurgery; Post, postsurgery; NS, not significant.
striction (to maintain MAP) rather than increase appendicular blood flow. Functional sympatholysis secondary to blockage of afferent information 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 those 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 enhance cerebral blood flow (17): whether this contributed to reduce central sympathetic outflow and/or increase exercise tolerance remains unknown. Fifth, we did not access any potential effects of TENS on postsurgery coronary blood flow (9, 10). Sixth, the study was underpowered to investigate differential effects on patients with and without a previous acute myocardial infarction. Finally, stellate ganglion blockade may 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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DISCLOSURES

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

AUTHOR CONTRIBUTIONS


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