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ORIGINAL ARTICLE

The Impact of Peripheral Nerve Stimulation on Coronary Blood Flow and Endothelial Function

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Abstract
Purpose The geko™ device is a small transcutaneous nerve stimulator that is applied non-invasively to the skin over the common peroneal nerve to stimulate peripheral blood flow. The purpose of this study was to investigate the effect of peripheral nerve stimulation on coronary flow dynamics and systemic endothelial function.
Methods We enrolled 10 male patients, age 59 ± 11 years, with symptomatic obstructive coronary disease undergoing percutaneous coronary intervention (PCI). Coronary flow dynamics were assessed invasively using Doppler flow wire at baseline and with nerve stimulation for 4 min. Measurements were taken in the stenotic coronary artery and in a control vessel without obstructive disease. At a separate visit, peripheral blood flow at the popliteal artery (using duplex ultrasound assessment) and endothelial function assessed by peripheral artery tonometry (PAT) were measured at baseline and after one hour of nerve stimulation.
Results Compared to baseline, there was a significant increase in coronary blood flow as measured by average peak velocity (APV) in the control vessel with nerve stimulation (20.3 ± 7.7 to 23.5 ± 10 cm/s; $p = 0.03$) and non-significant increase in the stenotic vessel (21.9 ± 12 to 23.9 ± 12.9 cm/s; $p = 0.23$). Coronary flow reserve did not change significantly. Reactive hyperemia-peripheral arterial tonometry (Rh-PAT) increased from 2.28 ± 0.39 to 2.67 ± 0.6, $p = 0.045$.
Conclusions A few minutes of peripheral nerve stimulation may improve coronary blood flow. This effect is more prominent in non-stenotic vessels. Longer stimulation improved endothelial function.

Keywords Angina · Endothelium · Blood flow · Coronary artery disease · Electrical stimulation

Clinical Trial Registration The study is registered at www.clinicaltrials.gov. Unique Identifier: NCT01853410, https://clinicaltrials.gov/ct2/show/NCT01853410.

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Introduction

Angina pectoris or anginal equivalent dyspnea are frequent symptoms related to an imbalance between myocardial blood supply and oxygen demand. Reduced myocardial blood flow in the setting of obstructive coronary artery disease can be improved through mechanical revascularization with percutaneous coronary intervention or bypass surgery.

Some patients may not be candidates for mechanical revascularization, and in these situations alternate methods are considered. One method is Enhanced External Counterpulsation (EECP). [1] Although the mechanism by which EECP reduces angina is not fully elucidated, it involves compression of peripheral blood vessels, thereby improving myocardial perfusion and coronary flow reserve. [2] In addition to immediate hemodynamic effects, EECP therapy has also been shown to improve markers of endothelial function. [3–5] A separate and different technique is the application of transcutaneous electrical nerve stimulation (TENS). Likely acting via neuromodulation pathways, it has been demonstrated previously that TENS can have potentially beneficial effects on coronary blood flow physiology. [6–10].

Other non-invasive therapies that improve venous return, may improve coronary flow as well. The geko™ device (FirskKind UK), is a small transcutaneous nerve stimulator that is applied to the skin over the common peroneal nerve in the lower limb and can stimulate blood flow in the venous system. By improving venous return, augmenting coronary blood flow, and potentially mitigating endothelial dysfunction, nerve stimulation has the potential to have a therapeutic effect in the management of coronary artery disease (CAD).

Endothelial dysfunction has been identified as an integral component of the systemic pathology evident in patients with cardiovascular disease. [11–13] Impaired endothelial function in this population is associated with an increased rate of adverse cardiovascular events. [12, 14] The mechanisms behind endothelial dysfunction in this patient group are likely multifactorial and a number of endogenous and exogenous modifiers have been identified. [15–17] Impaired blood flow mechanics that arise in the setting of vascular disease has been identified as potentiating mechanism that triggers endothelial dysfunction and promotes atherosclerosis and improvement in flow has been shown to improve endothelial function. [18, 19].

The purpose of the PERipheral stimulation device to improve Coronary flow reserve in Coronary Artery Disease (PERCCAD NCT01853410) study was to investigate the effect of peroneal nerve stimulation on coronary and peripheral blood flow as well as systemic endothelial function, in order to assess its potential role as a therapeutic modality for the treatment of symptomatic CAD.

Methods

Study Design

The PERCCAD study was a clinical pilot study assessing the effect of the peroneal nerve stimulation on coronary artery blood flow, peripheral blood flow and endothelial function. Patients acted as their own controls.

Patients

Ten patients were enrolled. Patients aged 18–80 years old undergoing elective percutaneous coronary intervention (PCI) were considered eligible. Patients were excluded if they had significant valvular heart disease or left ventricular dysfunction, contraindication to the administration of intracoronary adenosine, latex allergy or significant peripheral motor neuropathy. All studies were performed at the University Hospital campus of London Health Sciences Centre, London, ON, Canada. The Research Ethics Board of Western University approved the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Peroneal Nerve Stimulation

The geko device is a small transcutaneous nerve stimulator (weight 18 g, dimensions 149 mm × 42 mm × 11 mm) that is applied non-invasively to the skin over the common peroneal nerve in the lower limb (Fig. 1). The device is an electrical stimulator of the peroneal nerve that causes contraction of the calf muscles and has been demonstrated to safely stimulate blood flow from the gastrocnemius and soleus venous system. [20].

The geko device was fitted bilaterally behind the patients' knees in the popliteal fossa set to stimulate the common peroneal nerve transcutaneously. The device was activated during coronary flow assessment, peripheral artery assessment and endothelial function assessment. The device stimulates with a pulse frequency of 1 Hz and an electrical current of 1 mA. The intensity of the stimulation is altered by adjusting the device to one of seven pulse width settings (70, 100, 140, 200, 280, 400, 560 μs).

Coronary Flow Assessment

Prior to PCI, coronary flow velocities were measured using a 0.014″ Doppler tipped flow wire (FloWire®, Volcano Corporation, CA, USA). [21, 22] First a conventional guidewire was advanced into the coronary vessel within a micro catheter, and then the first guidewire was exchanged to the Doppler wire. The micro catheter was used to stabilize the Doppler wire and decrease artifact signal. Average peak velocity (APV) was recorded at baseline, with geko on a low pulse width setting (the threshold of a visible muscle twitch) after 2 min, and with geko at maximal setting (pulse width of 560 μs) after another 2 min. At each of these three time points coronary flow reserve (CFR) was assessed using intracoronary adenosine to induce hyperemia with 150 mcg for the left coronary artery and 120 mcg for the right coronary artery. [23, 24] Measurements of APV and CFR were performed first in a control artery (no stenosis above 30 % by visual assessment) and then the artery planned for PCI (prior to PCI). The LAD was used as control unless it was the culprit vessel. Intracoronary nitroglycerine (100 to 300 mcg) was administered prior to the adenosine administration to relieve any resting epicardial vessel spasm with an effect previously described to last for the duration of the measurements. [25] Since there is no data regarding the time required to achieve an effect, we chose stimulation durations that seemed reasonable to achieve immediate effect, without compromising patients safety.

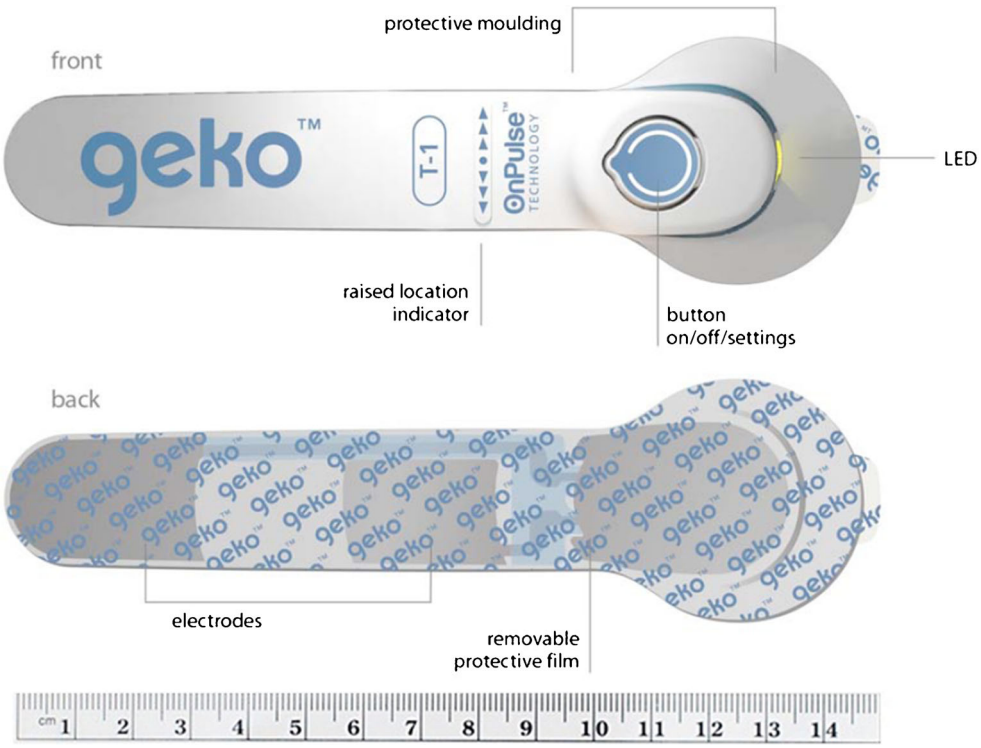

Fig. 1 The geko device (front and back) with ruler

Endothelial Function Assessment

The endothelial function assessment was performed on a separate visit following the PCI, by measurement of peripheral vasodilator response using fingertip pulse amplitude tonometry (peripheral arterial tonometry [PAT]). Subjects refrained from alcohol or products containing caffeine 24 h prior to the study. The study was performed after 15 min of rest, in a quiet, partially darkened room with an ambient temperature of 24 °C. PAT signals were obtained with the EndoPAT2000 (EndoPAT) device (Itamar Medical Inc., Caesarea, Israel). The EndoPAT has been previously validated as a method of endothelial function assessment. [12, 26] Proprietary finger probes were placed on the index finger of each patient's hand. Endothelial function is measured via a reactive hyperemia-peripheral arterial tonometry index (Rh-PAT index). The reactive hyperemia protocol consisted of a 5-min baseline measurement, after which a blood pressure cuff placed on the test arm was inflated to 60 mmHg above baseline systolic blood pressure, and at least 200 mmHg for 5 min. After 5 min, the cuff was deflated, and the PAT tracing recorded for a further 5 min. The ratio of the PAT signal after cuff release, compared to baseline, is calculated through a proprietary computer algorithm automatically normalizing for baseline signal, and indexed to the contra-lateral arm. The calculated ratio reflects the Rh-PAT index, a reflection of degree of endothelial function. Endothelial function was assessed at baseline and following one hour of continuous peroneal nerve stimulation with the stimulator set to a pulse width of 70–400 (medial 200) μs. The EndoPAT was used to calculate the RH-PAT index as described. Both EndoPAT tests were performed on the same day.

Peripheral Blood Flow

At the same visit as the endothelial function assessment, peripheral blood flow was measured at baseline and after one hour of exposure to the geko device. This was done using a 2D and Doppler derived ultrasound estimation of popliteal artery flow by recording the popliteal artery area and velocity at baseline and after one hour geko stimulation (with flow in ml/s calculated as area multiplied by velocity).

Study Sponsor

The study was investigator initiated. An unrestricted grant to cover the cost of the Doppler wires, and the geko devices was provided in kind by Firstkind Ltd. (United Kingdom). The manufacturers and distributers of the device had no role in study design, had no access to or control of the study data and were not involved in the drafting or revision of this manuscript nor did they have access to the manuscript prior to submission.

Objectives and Outcomes Measures

The primary objective of the PERCCAD study was to assess the effect of the peripheral nerve stimulation on coronary

blood flow in patients with symptomatic CAD who were undergoing percutaneous coronary intervention. Outcome measures for the primary outcome were APV and CFR.

The secondary objectives of the study were to assess the effect of nerve stimulation with the geko device on peripheral blood flow at the popliteal artery, and endothelial function as measured by Rh-PAT.

Statistical Analysis

Baseline variables are summarized by mean and standard deviation continuous variables and counts/percentages (categorical variables). Comparisons between before and after nerve stimulation were made using paired t test.

P-values are two-tailed and statistical significance was defined as $p < 0.05$ for all statistical comparisons.

Results

Ten patients were enrolled. Patient characteristics are shown in Table 1. Compared to baseline, there was a significant increase in APV in the control vessel with nerve stimulation from 20.3 ± 7.7 cm/s at baseline, to 21.0 ± 8.3 cm/s at low setting, and 23.5 ± 10 cm/s at maximal setting; $p = 0.03$ compared to baseline). Systolic blood pressure was 115 ± 20 mmHg at baseline and 130 ± 20 mmHg at maximal setting, $p = 0.004$. Heart rate was 66 ± 10 bpm at baseline and 62 ± 9 bpm with nerve stimulation, $p = 0.01$. Rate pressure product was 7582 ± 1405 at baseline and 7913 ± 1023 with nerve stimulation, $p = 0.63$.

There was no significant increase in APV in the stenotic vessel (21.9 ± 12 to 23.9 ± 12.9 cm/s; $p = 0.23$; Fig. 2). Systolic blood pressure during baseline measurements in the stenotic vessel was 116 ± 22 mmHg and 128 ± 18 mmHg, with nerve stimulation, $p = 0.007$. Heart rate was 64.5 ± 8 bpm at baseline and 62.6 ± 8.8 bpm with nerve stimulation, $p = 0.19$.

CFR in the control vessel was 2.2 ± 0.6 at baseline and 2.4 ± 0.6 with nerve stimulation ($p = 0.4$). CFR in the culprit vessel was 2.2 ± 0.9 at baseline and 1.9 ± 0.3 ($p = 0.4$) with stimulation.

One hour of peripheral nerve stimulation was associated with a statistically significant improvement in endothelial function as measured by EndoPAT (Fig. 3). During this test, the systolic blood pressure was 130.4 ± 12 mmHg at baseline and 131.1 ± 17.8 mmHg with one hour of nerve stimulation, $p = 0.88$, with not significant change in heart rate. Peripheral blood flow as measured by duplex popliteal artery vascular ultrasound increased in all patients except one, resulting in non-statistically significant increase between pre- and post-geko popliteal flow (Fig. 4). There was no correlation between the change in peripheral flow and change in Rh-PAT ($p = 0.95$).

Table 1 Baseline characteristics

Characteristic	N = 10
Age (mean ± SD* in years)	59.4 ± 10.8
Gender (% male)	100
Creatinine (mean ± SD in umol/l)	74.6 ± 13.9
Previous AMI† (%)	40
Previous PCI‡ (%)	50
Risk factors (%)	
Previous or current smoker	70
Hypertension	80
Dyslipidemia	100
Family History of CAD	50
Diabetes mellitus	30
Medications (%)	
Aspirin	100
Clopidogrel	100
ACE-I§ or ARB‖	80
Statin	90
Control vessel (%)	
LAD#	50
Diagonal	10
LCX**	30
RCA***	10
Culprit vessel (%)	
LAD	50
Diagonal	10
LCX	30
RCA	10

* SD – standard deviation

** *LCX* – left circumflex artery

*** *RCA* – right coronary artery

† *AMI* – acute myocardial infarction

‡ *PCI* – percutaneous coronary intervention

§ *ACE-I* – angiotension converting enzyme inhibitor

‖ *ARB* – angiotensin 2 receptor blocker

LAD – left anterior descending artery

Discussion

Impaired myocardial perfusion is a key mechanism in the induction of angina and myocardial dysfunction. Myocardial oxygen demand and microvascular performance are also important components in precipitating angina. When further revascularization is not an option, or standard therapies are insufficient to control symptoms, other novel therapies are attempted to improve myocardial blood supply and decrease angina. EECP devices have been demonstrated to augment cardiac performance and coronary flow and have a beneficial effect in reducing anginal symptoms in patients with coronary artery disease (CAD). [2, 5, 27, 28] However, this therapy

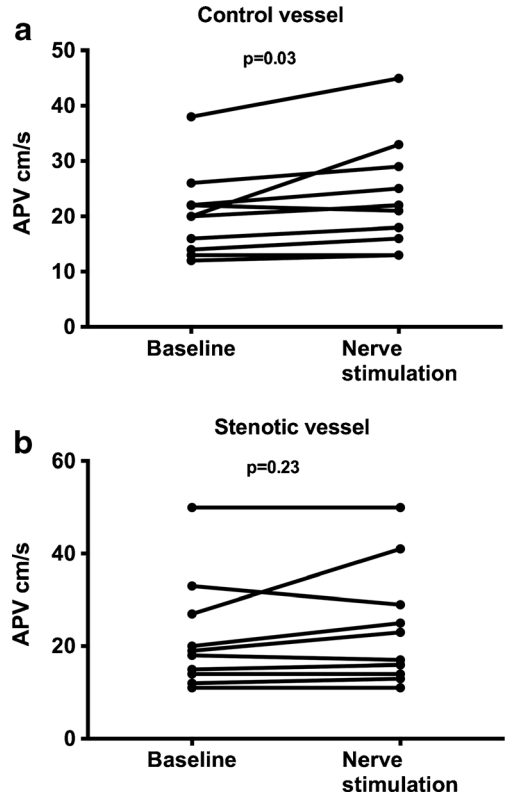

Fig. 2 Effect of nerve stimulation on coronary blood flow as measured by APV (average peak velocity) in control vessel (**a**) and stenotic vessel (**b**)

requires about 35 daily visits to specialized clinics and likely represents a key reason why EECP has not been adopted widely on an international basis. Transcutaneous (non-invasive) electrical nervous stimulation of skeletal muscle to improve venous return to the heart provides a potential mechanism to augment and improve blood flow, including coronary flow and may be a potential alternative method to achieve a similar effect. [20, 29, 30] In contrast to EECP, geko is less cumbersome and can be more easily integrated into clinical

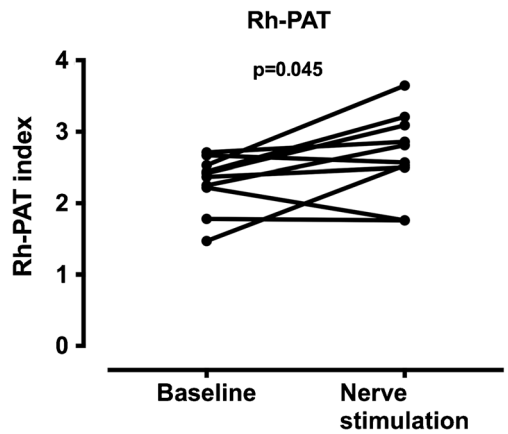

Fig. 3 Effect of one hour of peroneal nerve stimulation on endothelial function as measured by RH-PAT (reactive hyperemia-peripheral arterial tonometry) index

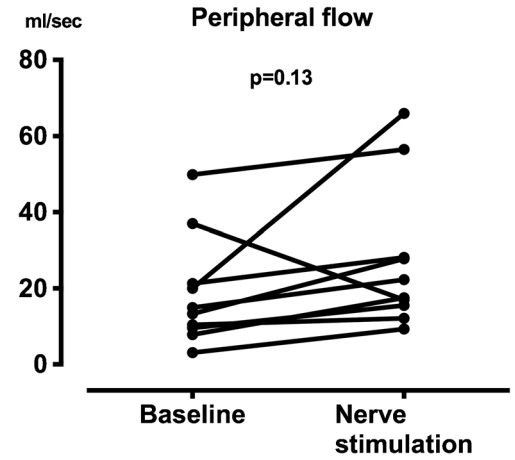

Fig. 4 Effect of nerve stimulation on blood flow in the popliteal artery

practice. Traditional TENS represents another mechanism by which modulation of coronary physiology may be achieved. At least some of the impact of geko on the cardiovascular system may be mediated primarily by regional neural pathways rather than the mechanical effect of muscle contraction.

Changes in Coronary Blood Flow and Coronary Reserve Assessment

The current study describes several hemodynamic effects of the peroneal nerve stimulation device. The device was associated with an improvement in coronary blood flow in non-stenotic vessels (using APV as a surrogate for flow, assuming no change in epicardial vessel diameter) but not in stenotic vessels. This has been described previously in patients treated with TENS and may improve coronary perfusion by optimizing collateral flow. [8] There was a significant increase in systolic blood pressure during nerve stimulation that may have contributed to the increase in coronary flow. The exact mechanism by which blood pressure was increased is unknown. Possibly it was related to an increase in venous return. However, we cannot exclude the possibility that this was related to patient stress response to sensation of nerve stimulation. The non-statistically significant reduction in heart rate that was observed may also have led to improved coronary flow by increasing LV diastolic filling but this is less clear. Blood pressure increased similarly during measurements in the obstructed and non-obstructed vessels. This suggests that coronary flow not limited by epicardial stenosis will improve with improved venous return, the likely mechanism by which the device improves coronary flow. Possibly the effect of nerve stimulation was not robust enough to affect flow in the obstructed vessels. The lack of change in CFR with or without nerve stimulation is not surprising because micro-vascular dysfunction would likely require an intervention of a much longer duration for CFR to be altered in any material way. [31].

Peripheral Blood Flow and Endothelial Dysfunction

Peripheral blood flow (as measured by duplex ultrasonography) increased in most patients with peroneal nerve stimulation. The lack of significant effect is likely a type 2 error related to small sample size, especially given the coronary flow findings.

Endothelial dysfunction continues to emerge as a key causative mechanism in coronary vascular disease. Patients with documented endothelial dysfunction have been demonstrated to have a higher preponderance of adverse cardiovascular events. The effect of geko to improve the RH-PAT index, a previously validated method of endothelial function assessment, represents a potential disease modifying mechanism given the association between endothelial dysfunction and adverse clinical outcomes. The effect on endothelial function was beyond an effect on blood pressure that was similar at baseline and following one hour of nerve stimulation.

We found an effect on endothelial function with 1 h of treatment, but no effect on CFR, after a few minutes of nerve stimulation. This discrepancy suggests that a longer duration of nerve stimulation may be required in order to achieve this type of hemodynamic effect. A more prolonged nerve stimulation intervention was technically not feasible at the time of PCI. Whether prolonged therapy, such as several weeks of therapy (comparable to EECP), would result in a clinical effect remains to be established.

Limitations

The current study was a relatively small pilot trial directed at assessing potential physiological responses of the cardiovascular system following peripheral nerve stimulation in patients with coronary artery disease. Only male patients were included, and therefore the results should be applied for males only. The small study size limits the power of the study to detect statistically significant effects of the device on vascular parameters. In the study, patients acted as their own controls and were not blinded to the therapy they were receiving. Outside of administering an otherwise medically not-indicated general anesthetic (which would raise significant ethical issues) blinding of participants was not possible because of the sensation the device causes. It is possible that sedation administered for the PCI procedure may have an impacted on the study findings. The measurements by Doppler are operator dependent, and subject to artifacts. Investigators were also not blinded, due to the presence of a visible muscle twitch with the geko device operating that could not practicably be hidden from the investigator involved. The investigator analyzing the data was also not blinded.

Conclusions

Peripheral nerve stimulation by electrical activation of the peroneal nerve was associated with improvements in invasively assessed coronary flow in non-stenotic coronary vessels as well as endothelial function. There was no effect on CFR. The results of this pilot study suggest a potential role for peripheral nerve stimulation to improve vascular physiology in patients with coronary disease and warrants further evaluation in larger clinical studies with clinical outcome parameters.

Compliance with Ethical Standards

Conflict of Interest The authors report no relationships that could be construed as a conflict of interest.

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