BMJ open
accessible medical research

Electrical modulation of the sympathetic nervous system in order to augment cerebral blood flow: a protocol for an experimental study

Mark Ter Laan,[1] J Marc C van Dijk,[1] Michiel J Staal,[1] Jan-Willem J Elting[2]

ABSTRACT

Introduction: Cerebral blood flow (CBF) is regulated by several mechanisms. Neurogenic control has been a matter of debate, even though several publications reported the effects of changes in sympathetic tone on CBF. Transcutaneous electrical nerve stimulation and spinal-cord stimulation have been shown to influence peripheral and cerebral blood flow through a sympathetic pathway. The authors hypothesise that certain pathological conditions result in a relative increase in the neurogenic regulation of CBF and that this regulation can be modulated electrically.

Methods and analysis: Patients with cerebral vasospasm after subarachnoid haemorrhage will be included. The experimental set-up measures several parameters that are involved in cerebral blood flow regulation in patients with cerebral vasospasm after subarachnoid haemorrhage. Measurements are taken at baseline and with stimulation in several frequencies. An ad hoc statistical analysis is used to evaluate different settings of the electrical stimulation. Autoregulation is evaluated with transfer function analysis and autoregulatory index calculations.

Ethics and dissemination: Ethical registration was granted by Medical Review Ethics Committee Groningen (ID METc 2010.123). All participants provide written informed consent on participation. Upon finishing a pilot study to investigate feasibility and effect, either future prospective (randomised) studies will be designed, or other modalities of electrical stimulation will be explored using the same set-up.

Trial Registration: Dutch Trial Registry: NTR2358.

ARTICLE SUMMARY

Article focus
- Although several papers have demonstrated neurogenic control of cerebral blood flow (CBF), the subject remains debatable. We postulate that neurogenic control of CBF is of importance in certain pathological circumstances.
- Electrical stimulation of the sympathetic nervous system has been shown to increase peripheral and cerebral bloodflow. We hypothesise that cervical trancutaneous electrical neurostimulation (TENS) can increase CBF.
- A study protocol is described to study the effects of CBF by cervical TENS.

Key messages
- The trial protocol described is being used in a pilot study but can be applied in future research.
- In particular, our mathematical and statistical analysis allows for an examination of the several settings of electrical stimulation.

Strengths and limitations of this study
- The study set-up takes into account as many factors as possible that influence CBF.
- TENS might not be feasible in troubled patients or patients with decreased consciousness.

[1]Department of Neurosurgery, University Medical Center Groningen, Groningen, The Netherlands
[2]Department of Neurophysiology and Neurology, University of Groningen, Groningen, The Netherlands

Correspondence to
Dr Mark Ter Laan;
m.ter.laan@nchir.umcg.nl

INTRODUCTION

Cerebral blood flow (CBF) is determined by cerebral perfusion pressure and cerebral vascular resistance (CVR) (figure 1). Both are regulated by complex mechanisms. Cerebral perfusion pressure depends on intracranial pressure (ICP) and mean arterial blood pressure (MAP), which in turn is a resultant of cardiac output and systemic vascular resistance. CVR is mainly regulated by cerebral vasomotor autoregulation, chemo-reflex control (based on arterial carbon dioxide and oxygen concentrations ($Paco_2$ and Pao_2)), local metabolic processes and nervous activity.[1−4] The anatomical and physiological bases of neurogenic control of CBF have been extensively studied. The cerebral vessels are thought to be directly sympathetically innervated in two ways: (1) extrinsic by the cervical sympathetic nervous system (analogous to other parenchymal vascular territories) and (2) intrinsic by central pathways of the locus coeruleus and other brainstem vasomotor centre origin.[2 5−7] Even though several studies have shown changes in CBF as a result of sympathetic

Figure 1 Regulatory mechanisms of cerebral blood flow. CBF, cerebral blood flow; CO, cardiac output; CPP, cerebral perfusion pressure; CVR, cerebral vascular resistance; ICP, intracranial pressure; MAP, mean arterial blood pressure; P, pulse; $PaCO_2$, arterial carbon dioxide pressure; PaO_2, arterial oxygen pressure; SV, stroke volume; SVR, systemic vascular resistance; $8/\pi \times \eta \times l/r^4$, Poiseuille's law; where η=blood viscosity, l=vessel length and r=vessel radius. Overlap and interactions between metabolic, chemical, neurogenic and vasomotor autoregulation are not shown.
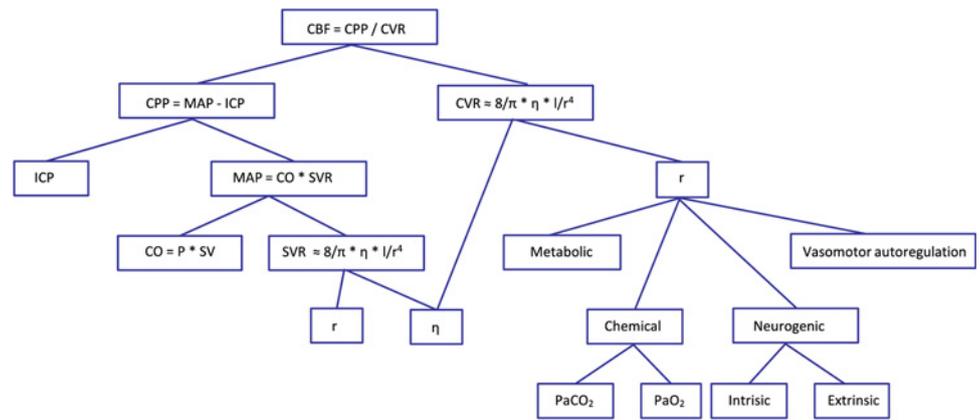
blockage or modulation in humans,[1] [8–12] the influence of the latter remains debatable.[13–16] In physiological resting conditions, the sympathetic effects on CVR seem to be minor, but in non-resting and particularly pathological conditions, the effects of sympathetic tone on CVR and consequently CBF become more apparent.[12] [17] [18] Indirect effects of the autonomic nervous system influence CBF by altering MAP, pulse and cardiac output—for example, through the arterial and cardiopulmonary baroreflexes.[11] [12]

All pathways can be affected by pathological conditions. Known examples are arterial hypertension, carotid stenosis, ischaemic or haemorrhagic cerebral vascular accidents, traumatic brain injury and cerebral vasospasm.[18–22] It is postulated that in pathological conditions, such as subarachnoid haemorrhage or ischaemic stroke, cerebral autoregulation is (focally) decreased, resulting in a relative increase in sympathetic regulation. Therefore, in these conditions, sympathetic pathways can be relevant, while in a normal resting state, they are over-ruled by stronger mechanisms. In these conditions, modulation of the sympathetic nerve activity on cerebral vessels could be of therapeutic importance.

In this context, electrical nervous stimulation is attractive, since several studies have shown the effects of electrical nervous stimulation on peripheral and cerebral blood flow. For example, it has been demonstrated that cervical spinal cord stimulation (cervical SCS) increases CBF,[23–25] which is thought to be caused by inhibition of the sympathetic nervous system[26] [27] and the release of vasoactive substances.[28] Both intrinsic and extrinsic systems have been postulated to be the path of action for cervical spinal cord stimulation induced increase in CBF.[27] [29] [30] Vascular calibre can directly reflect adrenergic tone and sympathetic receptor sensitivity, as demonstrated in experimental and animal models of vasospasm in SAH.[31] [32] Studies with spinal cord stimulation as a treatment of patients with coronary vasospasm showed ameliorated coronary perfusion independent of MAP, as did studies using transcutaneous electrical nerve stimulation (TENS).[33–35] Also, studies showed an inhibitory effect of TENS on sympathetically mediated reflexes.[36–38]

The decision to study the effects of TENS on CBF is empowered by the following motivations:
► Cervical SCS has the ability to increase CBF.[23–25] This effect must be indirect because the electrical field does not surpass the sympathetic pathways.[39]
► If the effect of SCS is indeed indirect, and (antidromic or orthodromic) neuronal pathways lead to modulation of sympathetic pathways in the spinal cord, then TENS may have the same effect.
► TENS may have a mild effect on reflexes involving the autonomic nervous system.[37]
► TENS and SCS are interchangeable in pain management, suggesting they affect similar pathways.
► TENS is non-invasive and safe.[40]

The aim of the study set-up is to investigate the following hypotheses:
► CBF can be influenced by electrical stimulation (either TENS or SCS) through the sympathetic nervous system.
► Neurogenic regulation of CBF is relatively increased when cerebral autoregulation is diminished in certain cerebrovascular diseases.

As a model, patients with cerebral vasospasm were selected, since, in those patients, the strong autoregulatory mechanisms are diminished by the disease. This makes them better candidates than healthy subjects with intact cerebral autoregulation in order to show proof of concept. Since cerebral vasospasm after SAH is often asymmetrical, these patients are ideal candidates to test both hypotheses at the same time. If we can show that autoregulation is asymmetrically impaired, and CBF can be electrically augmented on one side, a neurogenic pathway is likely to play a different role on each side.

METHODS AND ANALYSIS
Sample selection
The patient-selection criteria are listed in box 1. In order to study the feasibility of application of TENS in subjects

Box 1 Patient-selection criteria

Inclusion criteria
- Confirmed aneurysmatic subarachnoid haemorrhage
- Cerebral vasospasm demonstrated by transcranial Doppler, defined as a middle cerebral artery/internal carotid artery ratio >3
- Aneurysm is treated with a surgical or endovascular procedure
- Age >18 years
- Treatment can be started promptly
- Informed consent signed by patient or family

Exclusion criteria
- History of cervical spine or skull-base surgery
- Known adverse reaction to trancutaneous electrical neurostimulation pads
- Presence of any implanted electronic device (including pacemakers)
- Pre-existing disease that can obscure follow-up
- Unacceptable interference with ECG registration (in case intensive care is necessary)
- Insufficient temporal bony windows
- Use of sympathicomimetic or sympathicolytic agents

after SAH and in order to collect data for a future power analysis, a pilot study will be performed in 10 subjects.

Intervention
The subjects are treated with conventional TENS, providing a continuous flow of symmetrical rectangular biphasic pulses (Schwa Medico, Pierenkemper GMBH, Ehringhausen, Germany). Stimulation will be performed at 90% of the highest tolerated current, with a pulse-width of 200 μs. Stimulation frequencies are 20, 50, 100 and 120 Hz. In this way, the entire range of possible TENS frequencies and the most used frequencies in current TENS treatments are captured. Subjects are supine during the entire experiment. The TENS electrodes are applied cervical at the height of the mandible on both sides of the nuchal ligament (dermatome C2−C3).

Data collection and integration
An experimental set-up was designed to measure and influence the sympathetic regulatory mechanisms of CBF (by TENS). The set-up is planned to determine CBF (represented by cerebral blood-flow velocity), as well as to continuously monitor as many factors that influence CBF as possible (figure 1).

Data are collected using a continuous transcranial Doppler (TCD) monitor (DIGI-LITEtm, Raanana, Israel) to measure cerebral blood flow velocities (CBFV) in the middle cerebral artery (MCA) on both sides, a plethysmograph for assessing blood pressure and pulse (Finometer-Pro, Finapress Medical Systems, Amsterdam, The Netherlands), a capnograph (Capnomac Ultima, GE Healtcare, Chalfont St Giles, UK) to measure respiration rate and end-tidal carbon dioxide concentration

($ETCO_2$), and a near-infrared spectroscope (Invos 5100C, Somanetics, Troy, Michigan) to measure cerebral oxygenation. All analogue output is routed to a computer via a digitiser. The data are continuously registered using Labview 9.0 software. Raw data are sampled at 250 Hz. Beat-to-beat averages are calculated using the arterial blood pressure curve for triggering. To verify data quality and any relevant changes in all variables, both raw data and the calculated averages are plotted in waveform charts that are continuously updated. Both the raw data and the calculated averages will be stored in digital format on a PC for further off-line analysis.

Ad hoc statistical analysis
In order to determine the optimal frequency of stimulation, an ad hoc analysis is performed. Each time, a data stream acquired with a specific TENS frequency is compared with baseline. Stable sections of data of the same length with least artefacts will be selected for analysis after visual inspection. In order to clean the data from artefacts, the top and bottom 5% of data will be deleted, replacing those by linear interpolation using in-house written routines in the Matlab (6.5) environment. A visual inspection of the plotted filtered data will take place, and when necessary the same filter can be run a second time, or a data section with less noise will be selected.

Using the Matlab environment, matrices of data are compared with baseline using the Student t test, since a sufficient number of observations will be available. An effect size is calculated for the significant differences over time (with baseline as anchorpoint) in order to determine the frequency with the greatest amount of change since baseline. If none of the frequencies shows an effect of more than 20% of the pooled SD,[41] no superiority can be shown.

Analysis of autoregulation
Most patients will have more severe vasospasm on one side. This allows for a comparison of dynamic autoregulation.

Since the absolute values for MCA velocity can be influenced by many factors, including slight alteration of probe position and change in spontaneous autonomic activity, a frequency domain analysis will be performed. This is largely independent of minor fluctuations in the absolute values, since normalisation is used, and phase differences are less dependent on absolute values. This facilitates comparison of serial measurements.

The transfer function analysis[42] and the Autoregulatory Index (ARI) are evaluated,[43] estimated from spontaneous oscillations in blood pressure and TCD parameters, which results in a phase-difference parameter for the transfer function analysis, and an ARI index. Previously, values for the phase difference between the mean ABP and TCD values in the low-frequency range of >50° were suggested to represent intact cerebral autoregulation.[44 45] The values for the ARI index range from 0 to 9, with 9 indicating perfect autoregulation, and 0 meaning complete absence of autoregulation.

The beat-to-beat data are resampled at 10 Hz to create a uniform timebase. Also, the data are detrended, normalised and subtracted by 1, creating zero-mean signals. A Hanning window is applied to the data. Segments of data with 512 samples each are used to estimate the cross-spectra and transfer function between the mean ABP and TCD signals. Spectral averaging was employed using the Welch method, using segments with 50% overlap, which results in a spectral average that is calculated over at least nine segments of data (ie, five epochs of 51.2 s). The phase difference is determined in the 0.06−0.12 frequency range according to preset rules, provided coherence is >0.5.[42] Data on other frequency ranges will also be provided. For the ARI index, the inverse fast Fourier transform is calculated, using a cut-off frequency of 1.0 Hz. The first 10 s of the impulse response function is integrated to yield an estimate of the step response. The resulting curve is compared with the original Tiecks curves[46] by using a least-squares fitting procedure.

Interpretation

The described set-up is based on a few assumptions regarding several factors that play a role in CBF regulation. ICP probably remains constant during the experiments, even though fluctuations in CBF and venous pressure can affect ICP. We have no reason to suspect blood-viscosity changes during a measurement. We assume metabolic autoregulatory mechanisms to remain constant during the experiments; especially in our patients with cerebral vasospasm, we think they are absent. Oxygenation can be safely assumed to be constant when respiratory rate and room oxygen concentration remain constant. In order not to disturb these factors, all experiments take place in a quiet room and in a supine position.

Several factors (figure 1) have to be taken into account before the conclusion can be drawn that a change in CBFV measured in the MCA is most probably caused by a change in sympathetic activity. First of all, there should be no major changes in blood pressure and $Paco_2$ (represented by $ETco_2$ in our set-up), since changes in these variables can have a profound effect on CBFV. Furthermore, any large changes in pulse are also undesirable, since this might indicate a generalised sympathetic activation, and not a more focal sympathetic activation by TENS. Since we cannot be certain if the effects of TENS, if any, are mediated by the intrinsic or extrinsic sympathetic pathways, we can expect changes in vessel diameter of the MCA or the cerebral arterioles, or possibly even both.

CBF is determined indirectly by measuring CBFV in the MCA with TCD. In normal subjects, the MCA diameter is fairly constant, so flow velocity is proportional to cerebral flow, and arteriolar diameter is the most important regulator. If arteriolar diameter increases, resistance to flow will decrease, and CBFV (in the MCA) will increase, and vice versa. By contrast, in cerebral vasospasm, the opposite situation exists. In vasospasm, TCD measures intrastenotic blood-flow velocity, and blood-flow velocity is inversely related to CBF. In this situation, the relation CBFV=CBF/cross-sectional area can be applied, that is, if the MCA diameter increases, CBFV decreases.

Therefore, in this experiment, the finding of a decrease or increase in CBFV cannot be interpreted unambiguously. Based on TCD alone, even if we include indices of vascular resistance (pulsatility), we cannot determine with sufficient certainty if proximal or distal diameter changes may have occurred. We use the measurement of cerebral oxygenation (by NIRS) of the frontal lobe (downstream of the CBFV measurement in the MCA) as another modality to indirectly estimate changes in CBF. Provided brain metabolism, oxygen extraction, blood pressure and $Paco_2$ remain unaltered, an increase in oxygenation indicates vasodilatation and an increase in CBF, while a decrease indicates vasoconstriction and a decrease in CBF. Using both TCD and NIRS facilitates interpretation of data, provided the other factors remain stable (table 1). Once again, any substantial alterations in MAP, $ETco_2$ and pulse would make interpretation more difficult. Still, even though a raised $ETco_2$ or MAP can explain an increase in CBFV, a decrease in CBFV under these circumstances cannot be disregarded and must be explained otherwise.

ETHICS AND DISSEMINATION
Ethics and safety considerations
All potential participants will be informed fully about the study procedures and known risks. All subjects or their relatives will provide written informed consent. They will have the opportunity to withdraw from the study at any time.

Table 1 Theoretically possible measurements and the most probable consequences for vessel diameter, provided the mean arterial blood pressure and end tidal carbon dioxide concentration remain unchanged

Measurement		Vessel diameter		
Cerebral blood-flow velocity	Cerebral oxygen saturation	Middle cerebral artery	Arteriolar	Interpretation
↑	↓	↓	↔	Vasospasm increase
↑	↑	↔	↑	Arteriolar dilatation
↓	↑	↑	↔	Vasospasm decrease
↓	↓	↔	↓	Arteriolar constriction

Studies on SCS and CBF have produced no stimulation-related complications, only surgery-related complications such as infection, electrode displacement, etc. The TENS electrodes will be attached to the skin, which may cause skin irritation or rash comparable with sunburn. No serious adverse events are known from TENS in general. A previous study has reported that TENS can be safely applied in the cervical region.[40]

Our study protocol has been approved by the Medical Review Ethics Committee Groningen (ID METc 2010.123).

Dissemination

We hope to disseminate our study results through conferences and journal publications. If effects of TENS can be found in patients with cerebral vasospasm after SAH and TENS is shown to be a feasible application of electrical stimulation in this patient population, this set-up will be used in future prospective (randomised) controlled trials. If TENS is shown not to be feasible, other methods of neurostimulation such as subcutaneous electrical stimulation or spinal cord stimulation will be explored using the same set-up.

In conclusion, this set-up can be used to investigate regulation of CBF in several cerebrovascular diseases. Besides this, the application of ad hoc statistical analysis allows for the optimisation of several settings (frequency, current, etc) of electrical stimulation in one session, which facilitates research on electrical modulation of CBF.

REFERENCES

1. Ogoh S, Brothers RM, Eubank WL, et al. Autonomic neural control of the cerebral vasculature: acute hypotension. Stroke 2008;39:1979–87.
2. Sandor P. Nervous control of the cerebrovascular system: doubts and facts. Neurochem Int 1999;35:237–59.
3. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev 1959;39:183–238.
4. Mchedlishvili G. Physiological mechanisms controlling cerebral blood flow. Stroke 1980;11:240–8.
5. Edvinsson L, Hamel E. Perivascular nerves in brain vessels. In: Edvinsson L, Krause DN, eds. Cerebral Blood Flow and Metabolism. 2nd edn. Philadelphia, PA: Lippincott, Williams and Wilkins, 2002:43–67.
6. Hamel E. Perivascular nerves and the regulation of cerebrovascular tone. J Appl Physiol 2006;100:1059–64.
7. Goadsby PJ, Edvinsson L. Neurovascular control of the cerebral circulation. In: Edvinsson L, Krause DN, eds. Cerebral Blood Flow and Metabolism. 2nd edn. Philadelphia: Lippincott, Williams & Wilkins, 2002:172–88.
8. Treggiari MM, Romand JA, Martin JB, et al. Cervical sympathetic block to reverse delayed ischemic neurological deficits after aneurysmal subarachnoid hemorrhage. Stroke 2003;34:961–7.
9. Zhang R, Zuckerman JH, Iwasaki K, et al. Autonomic neural control of dynamic cerebral autoregulation in humans. Circulation 2002;106:1814–20.
10. Hamner JW, Tan CO, Lee K, et al. Sympathetic control of the cerebral vasculature in humans. Stroke 2010;41:102–9.
11. Jordan J, Shannon JR, Diedrich A, et al. Interaction of carbon dioxide and sympathetic nervous system activity in the regulationof cerebral perfusion in humans. Hypertension 2000;36:383–8.
12. Ogoh S, Ainslie PN. Cerebral blood flow during exercise: mechanisms of regulation. J Appl Physiol 2009;107:1370–80.
13. Strandgaard S, Sigurdsson ST. Last Word on Point:Counterpoint: Sympathetic nervous activity does/does not influence cerebral blood flow. J Appl Physiol 2008;105:1375.
14. Strandgaard S, Sigurdsson ST. Point:Counterpoint: Sympathetic activity does/does not influence cerebral blood flow. Counterpoint: Sympathetic nerve activity does not influence cerebral blood flow. J Appl Physiol 2008;105:1366–7; discussion 1367–8.
15. Van Lieshout JJ, Secher NH. Last Word on Point:Counterpoint: Sympathetic activity does/does not influence cerebral blood flow. J Appl Physiol 2008;105:1374.
16. Van Lieshout JJ, Secher NH. Point:Counterpoint: Sympathetic activity does/does not influence cerebral blood flow. Point: Sympathetic activity does influence cerebral blood flow. J Appl Physiol 2008;105:1364–6.
17. Dagal A, Lam AM. Cerebral autoregulation and anesthesia. Curr Opin Anaesthesiol 2009;22:547–52.
18. Paulson OB, Waldemar G, Schmidt JF, et al. Cerebral circulation under normal and pathologic conditions. Am J Cardiol 1989;63:2C–5C.
19. Lang EW, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. Crit Care Med 2001;29:158–63.
20. Aries MJ, Elting JW, De Keyser J, et al. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. Stroke 2010;41:2697–704.
21. Diehl RR. Cerebral autoregulation studies in clinical practice. Eur J Ultrasound 2002;16:31–6.
22. Panerai RB. Cerebral autoregulation: from models to clinical applications. Cardiovasc Eng 2008;8:42–59.
23. Clavo B, Robaina F, Catala L, et al. Increased locoregional blood flow in brain tumors after cervical spinal cord stimulation. J Neurosurg 2003;98:1263–70.
24. Takanashi Y, Shinonaga M. Spinal cord stimulation for cerebral vasospasm as prophylaxis. Neurol Med Chir (Tokyo) 2000;40:352–6; discussion 356–7.
25. Clavo B, Robaina F, Catala L, et al. Effect of cervical spinal cord stimulation on regional blood flow and oxygenation in advanced head and neck tumours. Ann Oncol 2004;15:802–7.
26. Linderoth B, Herregodts P, Meyerson BA. Sympathetic mediation of peripheral vasodilation induced by spinal cord stimulation: animal studies of the role of cholinergic and adrenergic receptor subtypes. Neurosurgery 1994;35:711–19.
27. Goellner E, Slavin KV. Cervical spinal cord stimulation may prevent cerebral vasospasm by modulating sympathetic activity of the superior cervical ganglion at lower cervical spinal level. Med Hypotheses 2009;73:410–13.
28. Goksel HM, Karadag O, Turaclar U, et al. Nitric oxide synthase inhibition attenuates vasoactive response to spinal cord stimulation in an experimental cerebral vasospasm model. Acta Neurochir (Wien) 2001;143:380–90; discussion 390–1.
29. Patel S, Huang DL, Sagher O. Sympathetic mechanisms in cerebral blood flow alterations induced by spinal cord stimulation. J Neurosurg 2003;99:754–61.
30. Patel S, Huang DL, Sagher O. Evidence for a central pathway in the cerebrovascular effects of spinal cord stimulation. Neurosurgery 2004;55:201–6; discussion 206.
31. Edvinsson L, Gulbenkian S, Barroso CP, et al. Innervation of the human middle meningeal artery: immunohistochemistry, ultrastructure, and role of endothelium for vasomotility. Peptides 1998;19:1213–25.
32. Endo S, Suzuki J. Experimental cerebral vasospasm after subarachnoid hemorrhage. Participation of adrenergic nerves in cerebral vessel wall. Stroke 1979;10:703–11.
33. Jessurun GA, Hautvast RW, Tio RA, et al. Electrical neuromodulation improves myocardial perfusion and ameliorates refractory angina pectoris in patients with syndrome X: fad or future? Eur J Pain 2003;7:507–12.

34. Sanderson JE, Woo KS, Chung HK, *et al*. The effect of transcutaneous electrical nerve stimulation on coronary and systemic haemodynamics in syndrome X. *Coron Artery Dis* 1996;7:547−52.
35. Hautvast RW, Ter Horst GJ, DeJong BM, *et al*. Relative changes in regional cerebral blood flow during spinal cord stimulation in patients with refractory angina pectoris. *Eur J Neurosci* 1997;9:1178−83.
36. Emanuelsson H, Mannheimer C, Waagstein F, *et al*. Catecholamine metabolism during pacing-induced angina pectoris and the effect of transcutaneous electrical nerve stimulation. *Am Heart J* 1987;114:1360−6.
37. Sanderson JE, Tomlinson B, Lau MS, *et al*. The effect of transcutaneous electrical nerve stimulation (TENS) on autonomic cardiovascular reflexes. *Clin Auton Res* 1995;5:81−4.
38. Mannheimer C, Carlsson CA, Emanuelsson H, *et al*. The effects of transcutaneous electrical nerve stimulation in patients with severe angina pectoris. *Circulation* 1985;71:308−16.
39. Oakley JC, Prager JP. Spinal cord stimulation: mechanisms of action. *Spine (Phila Pa 1976)* 2002;27:2574−83.
40. Ter Laan M, van Dijk JM, Elting JW, *et al*. The influence of transcutaneous electrical neurostimulation (TENS) on human cerebral blood flow velocities. *Acta Neurochir (Wien)* 2010;152:1367−73; discussion 1373.
41. Middel B, Stewart R, Bouma J, *et al*. How to validate clinically important change in health-related functional status. Is the magnitude of the effect size consistently related to magnitude of change as indicated by a global question rating? *J Eval Clin Pract* 2001;7:399−410.
42. Reinhard M, Muller T, Guschlbauer B, *et al*. Transfer function analysis for clinical evaluation of dynamic cerebral autoregulation−a comparison between spontaneous and respiratory-induced oscillations. *Physiol Meas* 2003;24:27−43.
43. Panerai RB. Transcranial Doppler for evaluation of cerebral autoregulation. *Clin Auton Res* 2009;19:197−211.
44. Immink RV, van den Born BJ, van Montfrans GA, *et al*. Impaired cerebral autoregulation in patients with malignant hypertension. *Circulation* 2004;110:2241−5.
45. Immink RV, van Montfrans GA, Stam J, *et al*. Dynamic cerebral autoregulation in acute lacunar and middle cerebral artery territory ischemic stroke. *Stroke* 2005;36:2595−600.
46. Tiecks FP, Lam AM, Aaslid R, *et al*. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 1995;26:1014−19.