Remodelling of cardiac sympathetic re-innervation with thoracic spinal cord stimulation improves left ventricular function in a porcine model of heart failure

Song-Yan Liao†, Yuan Liu†, Mingliang Zuo†, Yuelin Zhang, Wensheng Yue, Ka-Wing Au, Wing-Hon Lai†, Yangsong Wu, Chika Shuto, Peter Chen, Chung-Wah Siu, Peter J Schwartz, and Hung-Fat Tse

1Cardiology Division, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China; 2Center for Innovation and Strategic Collaboration, St Jude Medical, Inc, St Paul, MN, USA; 3Research Center of Heart, Brain, Hormone and Healthy Aging, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; 4IRCCS Istituto Auxologico Italiano, Center for Cardiac Arrhythmias of Genetic Origin, Milan, Italy; and 5Shenzhen Institutes of Research and Innovation, University of Hong Kong, Hong Kong, China

Received 2 October 2014; accepted after revision 30 December 2014; online publish-ahead-of-print 12 March 2015

Aims
Thoracic spinal cord stimulation (SCS) has been shown to improve left ventricular ejection fraction (LVEF) in heart failure (HF). Nevertheless, the optimal duration (intermittent vs. continuous) of stimulation and the mechanisms of action remain unclear.

Methods and results
We performed chronic thoracic SCS at the level of T1–T3 (50 Hz, pulse width 0.2 ms) in 30 adult pigs with HF induced by myocardial infarction and rapid ventricular pacing for 4 weeks. All the animals were treated with daily oral metoprolol succinate (25 mg) plus ramipril (2.5 mg), and randomized to a control group (n = 10), intermittent SCS (4 h × 3, n = 10) or continuous SCS (24 h, n = 10) for 10 weeks. Serial measurements of LVEF and +dP/dt and serum levels of norepinephrine and B-type natriuretic peptide (BNP) were measured. After sacrifice, immunohistological studies of myocardial sympathetic and parasympathetic nerve sprouting and innervation were performed. Echocardiogram revealed a significant increase in LVEF and +dP/dt at 10 weeks in both the intermittent and continuous SCS group compared with controls (P < 0.05). In both SCS groups, there was diffuse sympathetic nerve sprouting over the infarct, peri-infarct, and normal regions compared with only the peri-infarct and infarct regions in the control group. In addition, sympathetic innervation at the peri-infarct and infarct regions was increased following SCS, but decreased in the control group. Myocardium norepinephrine spillover and serum BNP at 10 weeks was significantly decreased only in the continuous SCS group (P < 0.05).

Conclusions
In a porcine model of HF, SCS induces significant remodelling of cardiac sympathetic innervation over the peri-infarct and infarct regions and is associated with improved LV function and reduced myocardial norepinephrine spillover.

Keywords
Spinal cord stimulation • Heart failure • Sympathetic innervation

Introduction
It is well known that imbalance of the autonomic nervous system with increased sympathetic and decreased parasympathetic tone has been observed in patients with heart failure (HF), and is associated with progressive left ventricular (LV) dysfunction and increased mortality. As a result, different therapeutic approaches have been proposed to reverse this dysregulation of the autonomic nervous system. Spinal cord stimulation (SCS) with an implantable device has been used for a decade to relieve angina in patients with severe coronary artery disease. Although the mechanisms remain unclear, prior studies in large animal models of HF have demonstrated that short-term thoracic
What’s new?

- Either intermittent or continuous spinal cord stimulation (SCS) results in improvement in left ventricular (LV) contractile function as determined by echocardiographic and invasive haemodynamic assessment in a porcine model of ischaemic HF. While there was no significant difference in the improvement in LV function for both SCS groups, continuous SCS rather than intermittent SCS appears to prevent progressive dilatation of LV end-systolic and end-diastolic diameters.
- While medical therapies with ACE-I and β-blocker reduce the serum norepinephrine level, only continuous SCS significantly decreased the serum level of BNP and myocardial norepinephrine spillover.
- Chronic SCS induced significant remodelling of the cardiac sympathetic myocardial innervation with diffuse and more homogenous sympathetic nerve sprouting and sympathetic re-innervation over infarct and peri-infarct regions, without changes in the pattern of parasympathetic innervation after chronic SCS.
- Chronic SCS increased myocardial expression of SERCA-2a mRNA and protein.

SCS reduces the incidence of ventricular tachyarrhythmias (VT) induced by acute myocardial ischaemia, and improves LV contractile function without increasing myocardial oxygen consumption. Chronic intermittent thoracic SCS in a canine model of HF also improved the LV ejection fraction (LVEF) beyond that achieved with angiotensin-converting enzyme inhibitor (ACE-I) and β-adrenergic receptor blockade, and reduced the risk of spontaneous VT. Nevertheless, it is unclear whether chronic continuous rather than intermittent stimulation can further improve the therapeutic efficacy of SCS.

Cardiac sympathetic denervation as determined by 123I-metaiodobenzylguanidine (123I-MIBG) scintigraphy has been shown to be associated with an increased risk of HF progression, arrhythmic events, and cardiac death in patients with symptomatic HF and low LVEF. Regional sympathetic denervation can contribute to impaired myocardial contraction and induce LV mechanical dysynchrony. Prior experimental studies have shown that chronic electrical neuronal stimulation has neurotrophic effects and can promote nerve growth.

In this study, we sought to compare the therapeutic efficacy of chronic intermittent vs. continuous SCS in a porcine model of HF, and investigated whether chronic thoracic SCS can improve LVEF by promoting sympathetic re-innervation of the dysfunctional myocardium.

Methods

Study protocol

The study protocol is summarized in Figure 1. Male or female pigs weighing 35–45 kg (9–12 months old) were used for this study. An animal model of post-myocardial infarction (MI) and rapid pacing to induce HF was created as described previously.

In brief, all animals were anaesthetized with tiletamine and zolazepam (zolletil 20 mg/kg i.m.). Endotracheal intubation was performed and anaesthesia maintained with a propofol infusion. Acute MI was induced in all animals by coronary artery embolization at the left circumflex artery, followed by 4 weeks of rapid right ventricular pacing (150 b.p.m.) using an TVI pacemaker to induce HF. After ventricular pacing had ceased for 24 h, repeat echocardiographic and invasive haemodynamic assessments were performed. Animals with impaired LVEF (≤45%) were randomized to receive medication alone (control group, n = 10), intermittent SCS + medication (4 h x 3, n = 10), or continuous SCS + medication (24 h, n = 10) for 10 weeks. During this period, all the animals were treated with daily oral metoprolol succinate (25 mg) plus ramipril (2.5 mg). Animals randomized to the SCS groups underwent SCS implantation. All animal experiments complied with the requirements of the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health and the study protocol was approved by the local institutional ethics committee for animal research.

Electrocardiographic parameters, including resting heart rate, PR interval, QRS duration, and corrected QT interval (based on Bazett’s correction); and serum biomarkers, including B-type natriuretic peptide (BNP) and norepinephrine level, were measured at baseline, immediately post-MI, and before and after 10 weeks of chronic SCS.

Spinal cord stimulator implantation

All SCS group animals underwent spinal cord stimulator lead and pulse generator implantation using a commercially available neurostimulation system (Eon Mini Neurostimulation System, St Jude Medical) under sterile conditions and X-ray guidance. Animals were placed in a left lateral position following induction of anaesthesia with propofol infusion. A 14-gauge epidural needle was used to access the epidural space at level T10–L2, and two octropolar electrodes (Octrode, St Jude Medical) were inserted. The tips of the electrodes were advanced under fluoroscopic guidance to T1–3 level to achieve stimulation of both effenter and afferent sympathetic fibres (Figure 1A). The leads were tunnelled subcutaneously below the left costal arch and connected to a permanent pulse generator placed in a subcutaneous pocket in the lateral abdominal region. Stimulation pulses were initiated at 2 Hz, 0.2 ms, with the amplitude gradually increased until shoulder motion and muscle twitching was observed. The stimulation threshold was determined as the lowest output required for a muscle response (range 0.1–10 mA). Chronic SCS was performed at 90% of the motor threshold at 50 Hz and pulse width 0.2 ms; this has been shown to provide optimal SCS.

Invasive haemodynamic assessment

Invasive haemodynamic assessment was performed during induction of MI, and before and 10 weeks following SCS to assess changes in LV function. In brief, a 7-Fr combined catheter micromanometer (Millar Instruments, Houston, TX, USA) was calibrated in isotonic saline with a pressure–volume signal processor (CD Leycom, The Netherlands), then advanced via the carotid or femoral artery to the LV apex for the measurement of LVEDV/EDV and –ve dP/dt.8,14

Echocardiographic measurements

Standard transthoracic echocardiogram including 2D and M-mode imaging was performed at baseline, post-MI, and before and 10 weeks following SCS using a commercially available echocardiographic system (Vivid i, GE Vingmed, Horten, Norway) equipped with a 3–9 MHz transducer. In each animal, the standard 2D and M-mode echocardiography was performed to measure LVEF and LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD). All echocardiographic measurements were interpreted off-line in a blinded fashion using a computer workstation (GE Medical, EchoPac, Horten, Norway).
Biomarker assessment
Serum porcine BNP level (Phoenix Pharmaceuticals, Burlingame, CA, USA) and norepinephrine (Rocky Mountain Diagnostics, Boulder, CO, USA) were measured in the peripheral arterial blood using ELISA kits to assess HF status and peripheral sympathetic activation, respectively. Coronary sinus blood samples were also obtained before and after SCS to measure myocardial norepinephrine spillover.

Histology and immunohistochemical assessment
Detailed histological and immunohistochemical assessment were performed to determine the effect of chronic SCS. All animals were anesthetized with tiletamine and zolozepam (zoletil 20 mg/kg i.m.), then sacrificed by i.v. bolus injection of 100 mmol of potassium chloride after 10 weeks of follow-up. Their hearts were removed and cut into eight sections (7–10 mm thick) perpendicular to the apical–basal axis. The sections of LV were traced and colour photographs of each section were obtained to provide a permanent record. Planimetry of the tracings was performed to measure infarct size (as a percentage of the LV mass). Portions of the slices that contained infarcted myocardium were selected, from which approximate 1 cm² pieces within (infarct region), adjacent (peri-infarct region), and remote (normal region) to the infarct site were sectioned for histological examination and immunohistochemical evaluation.

Cardiac sympathetic and parasympathetic nerve sprouting and innervation were studied using immunohistochemical techniques. Immunostaining for nerve markers: tyrosine hydroxylase (TH), acetylcholinesterase (AChE), growth-associated protein 43 (GAP-43) and neuronal marker: protein gene product 9.5 (PGP-9.5) was performed at five random sites in the infarct, peri-infarct, and normal region. Paraffin sections (4 μm) were cut from the same regions and then de-paraffinized, rehydrated, and incubated in 10% normal goat serum (Vector Lab, Burlingame, CA, USA). Anti-GAP-43, anti-TH, anti-ChAT, and anti-PGP-9.5 antibodies [rabbit polyclonal anti-GAP-43, anti-TH, anti-AChE (Millipore, Inc., USA), and anti-PGP-9.5 (Lifespan Bioscience, USA), 1:250, respectively] were used for immunocytochemical staining. In each animal, two random samples were taken from each of the infarct, peri-infarct and normal regions. For each slide, five regions were randomly selected and examined at ×400 magnification. The results were expressed as the number of positive cells per mm². All the measurements were counted in a blinded fashion.

Statistical analysis
All data are expressed as mean ± SEM, and analysis was performed using the SPSS software (SPSS, Inc., Chicago, IL, USA). Comparison of serial changes in echocardiographic and invasive LV hemodynamic parameters, and biomarkers at different time points between the control, intermittent SCS, and continuous SCS groups, as well as the immunohistological staining results were made using two-way repeated analysis of variance with Tukey’s test as appropriate. Statistical significance was defined at a value of P < 0.05.

Results
We induced acute MI in 52 pigs, 16 of whom died within 2 days. The remaining 36 animals underwent rapid ventricular pacing to induce HF, and 30 animals with impaired LVEF < 45% (MI + HF) documented on echocardiogram were studied. These animals were randomized to the control (n = 10), intermittent SCS (n = 10), or continuous SCS groups (n = 10).

Electrocardiographic data
There were no significant differences between the control and SCS-treated groups in electrocardiographic parameters, including
resting heart rate (Figure 2A), PR interval (Figure 2B), QRS duration (Figure 2C) and corrected QT interval (Figure 2D) at baseline, post-myocardial infarction (MI), after induction of heart failure (MI + HF), and during spinal cord stimulation (SCS) in control (n = 10); intermittent SCS (n = 10) and continuous SCS (n = 10) groups.

Echocardiographic data
After pacing was turned off for 24 h, echocardiogram showed that LVEF significantly decreased from 63.7 ± 0.8% at baseline to 37.1 ± 1.3% after induction of MI + HF (P < 0.01). This confirmed establishment of an animal model of HF. As shown in Figure 2A, there were no differences in LVEF at baseline, following MI and during MI + HF between the control and SCS-treated groups (P > 0.05). At the 10-week follow-up, there was no change in LVEF compared with MI + HF in the control group (P > 0.05). In contrast, LVEF significantly increased at the 10-week follow-up in both the intermittent and the continuous SCS groups when compared with the MI + HF status and control group (Figure 3A, P < 0.05). There was nonetheless no difference between the intermittent and continuous SCS groups (Figure 3A, P > 0.05).

In all three groups, LVESDs (Figure 3B, P < 0.05) and LVEDDs (Figure 3C, P < 0.05) significantly increased during the MI + HF status compared with baseline. At 10-week follow-up, the LVESDs and LVEDDs in the control group and the intermittent SCS group, but not the continuous SCS group, remained increased compared with baseline. Nonetheless, there were no differences in LVESD (Figure 2B, P > 0.05) and LVEDD (Figure 2C, P > 0.05) between the three groups at the 10-week follow-up.

Haemodynamic data
Compared with baseline, LV systolic contractile function as determined by LV + dP/dt significantly decreased following MI and during MI + HF in all three groups (Figure 3D). In the control group, there was no change in LV + dP/dt at the 10-week follow-up compared with MI + HF (P > 0.05). In contrast, LV + dP/dt significantly increased at the 10-week follow-up in both the intermittent SCS and the continuous SCS groups compared with the corresponding MI + HF status and LV + dP/dt at the 10-week follow-up in the control group (Figure 3D, all P < 0.05). Compared with baseline, LV − dP/dt significantly decreased after MI and during MI + HF in the control, the intermittent SCS, and the continuous SCS groups (Figure 3E, all P < 0.05). There were no differences in LV − dP/dt between the three groups at the 10-week follow-up (Figure 3E, all P > 0.05).

Biomarker data
Serial changes in serum BNP and norepinephrine in the control, intermittent, and continuous SCS groups showed similar trends in which
their level progressively increased compared with baseline following induction of MI + HF (Figure 4A, P < 0.05). At the 10-week follow-up, both the serum BNP and norepinephrine level in all three groups was lower, although significantly decreased only in the continuous SCS group compared with their MI + HF status. The coronary sinus level of norepinephrine remained elevated at 10 weeks in the control group compared with MI + HF. In contrast, the coronary sinus level of norepinephrine was decreased at the 10-week follow-up in the continuous SCS group compared with MI + HF (Figure 4B). At the 10-week follow-up, the serum BNP level, and the serum and coronary sinus level of norepinephrine was significantly lower in the continuous SCS group than the control group (Figure 4B, P < 0.05). As determined by RT–PCR, the expression of BNP mRNA at the infarct region was significantly higher than that at the normal region in the control group (Figure 4C, P < 0.05). The expression of norepinephrine receptor mRNA at the infarct region was significantly higher than that at the normal region in the continuous SCS group (Figure 4D, P < 0.05). Indeed, significant decreased expression of BNP mRNA (Figure 4C) and increased expression of norepinephrine receptor mRNA (Figure 4D) were observed at the infarct region in the continuous SCS group compared with the control group.

Expression of GAP-43 protein is associated with nerve sprouting.\textsuperscript{14,16} Immunohistochemical staining revealed increased GAP-43-positive nerves at the peri-infarct and infarct regions compared with the normal region in the control group (Figure 5A, P < 0.05), suggesting heterogeneous nerve sprouting following induction of MI + HF (Supplementary material online, Figure S1). In contrast, diffuse increased GAP-43 positive nerves were observed at the normal, peri-infarct, and infarct regions in both SCS-treated groups. There were no significant differences in the number of GAP-43-positive nerves among the infarct, peri-infarct, and normal regions in the intermittent and continuous SCS groups (Figure 5A, P > 0.05). Compared with the control group, the number of GAP-43-positive nerves was significantly higher in the SCS-treated groups compared with the normal region (Figure 5A, P < 0.05). Moreover, the number of GAP-43-positive nerves was significantly higher at the infarct region in the continuous SCS group compared with the control and the intermittent SCS groups (Figure 5A, P < 0.05) (Supplementary material online, Figure S1).

PGP9.5 is a general neuronal marker that signifies myocardial innervation.\textsuperscript{17} Immunohistochemical staining showed decreased PGP9.5-positive cells at the infarct regions compared with the normal region in the control group (Figure 5B, P < 0.05), suggesting nerve denervation at the infarct region following induction of MI + HF (Supplementary material online, Figure S2). While there were no differences at the normal region between the three groups, the number of PGP9.5-positive cells was significantly increased at the peri-infarct and infarct regions in both SCS-treated groups compared with the normal region (Figure 5B, P < 0.05). In addition, the number

**Histology and immunohistochemical data**

Histological examination revealed a similar percentage area of infarct size for the control, intermittent SCS, and continuous SCS groups (13.0 ± 0.7 vs. 12.3 ± 0.5 vs. 11.5 ± 0.6%, P = 0.5).

Figure 3 Serial measurements of (A) left ventricular ejection fraction (LVEF); (B) LVEDD; (C) LVESD; (D) left ventricular (LV) +dP/dt; and (E) –dP/dt in animals at baseline, post-myocardial infarction (MI), after induction of heart failure (MI + HF), and during SCS in control (n = 10); intermittent SCS (n = 10) and continuous SCS (n = 10) groups.
of PGP9.5-positive cells at the peri-infarct and the infarct regions was significantly higher in both SCS-treated groups compared with the control group (Figure 5B, \(P < 0.05\)). There was no significant difference in the number of PGP9.5-positive cells at different regions between the continuous and intermittent SCS groups (\(P > 0.05\)) (Supplementary material online, Figure S2).

Tyrosine hydroxylase is a rate-determining enzyme for catecholamine synthesis and thus a sympathetic nerve marker.\(^{14,16,17}\) Immunohistochemical staining revealed increased TH-positive cells at the peri-infarct and the infarct region in all three groups compared with their normal region (Figure 5C, \(P < 0.05\)) (Supplementary material online, Figure S3). Further, the number of TH-positive cells at the infarct regions was significantly higher in the SCS-treated groups than the control group (Figure 5C, \(P < 0.05\)). Nevertheless, there was no significant difference in the number of TH-positive cells at the peri-infarct and infarct regions in all three groups compared with their normal regions (Figure 5D, \(P > 0.05\)) (Supplementary material online, Figure S4).

Immunohistochemical staining for AChE was used as a parasympathetic nerve marker.\(^{16}\) The number of AChE positive cells was increased at the peri-infarct and the infarct regions in all three groups compared with their normal regions (Figure 5D, \(P < 0.05\)) (Supplementary material online, Figure S4). The number of AChE positive cells was also higher at the infarct regions in all three groups compared with their peri-infarct regions (Figure 5D, \(P < 0.05\)). Nevertheless, there was no significant difference in the number of AChE positive cells at the infarct, peri-infarct, and normal regions among the three groups (Figure 5D, \(P > 0.05\)) (Supplementary material online, Figure S4).

As shown in Figure 5E, the expression of SERCA-2a mRNA and protein as determined by RT–PCR and western blot, respectively, was significantly reduced at the peri-infarct and infarct regions compared with the normal regions in the control group (Figure 5E, \(P < 0.05\)). In contrast, the expression of SERCA-2a mRNA and protein was decreased only at the infarct region, not the peri-infarct region, compared with the normal regions in the SCS-treated groups. Compared with the control group, the expression of SERCA-2a mRNA and protein was significantly increased at the normal, peri-infarct, and infarct regions in the SCS-treated groups (Figure 5E, \(P < 0.05\)). Nevertheless, comparison of the continuous and intermittent SCS groups revealed no significant differences (\(P > 0.05\)).
Figure 5  Immunohistochemical staining for (A) growth-associated protein 43 (GAP-43); (B) protein gene product 9.5 (PGP-9.5); (C) tyrosine hydroxylase (TH); and (D) AChE at five random sites at the normal, peri-infarct, and infarct regions in the control (n = 10), intermittent (n = 10) and continuous SCS groups (n = 10). (E) Tissue expression of mRNA and protein levels in densitometric units of sarcoplasmic reticulum Ca2+ ATPase (SERCA-2a) as determined by RT–PCR and western blots at the normal, peri-infarct, and infarct regions in the control (n = 4), intermittent (n = 4), and continuous SCS groups (n = 4).
Discussion

The major findings of this study are that (i) both intermittent and continuous chronic SCS result in improved LV contractile function as determined by echocardiographic and invasive haodynamic assessment in a porcine model of ischaemic HF. Although there was no significant difference in the improvement in LV function between the two SCS groups, continuous SCS rather than intermittent SCS appears to prevent progressive dilatation of LVESD and LVEDD; (ii) although pharmacotherapy with ACE-I and β-blocker reduced the serum norepinephrine level, only continuous SCS significantly decreased the serum level of BNP and myocardial norepinephrine spillover; (iii) chronic SCS induced significant remodelling of the cardiac sympathetic myocardial innervation with diffuse and more homogenous sympathetic nerve sprouting; and sympathetic re-innervation over the infarct and peri-infarct regions; (iv) there were no significant changes to the pattern of parasympathetic innervation after chronic SCS; and (v) chronic SCS increased myocardial expression of SERCA-2a mRNA and protein. Taken together, our findings offer a novel insight that chronic SCS induces remodelling of sympathetic nerve sprouting and re-innervation in heart failure without any change in vagal activity. These changes in cardiac sympathetic innervation are associated with decreased norepinephrine spillover, and enhanced SERCA-2a expression in the failing myocardium that could contribute to the improved LV contractile function following chronic SCS.

Our results provide novel insights into the potential mechanisms by which SCS improves LV function in HF. It has been postulated that long-term modulation of the imbalance between sympathetic and parasympathetic activity should be the target of autonomic interventions. This is clearly true for vagal stimulation and also for SCS. In this study, we observed a significant increase in resting heart rate in all three groups at the 10-week follow-up, with no differences between the SCS-treated group and control group. This might be attributed to the termination of rapid pacing in the post-MI HF model used in this study, as well as the lack of changes in the pattern of parasympathetic innervation in the control group and following chronic SCS. Prior experiments demonstrated that chronic electrical neuronal stimulation has significant neurotropic effects, such as the expression of nerve growth factor, that can promote nerve growth in both normal and infarcted myocardium. In concordance with the results of previous studies, we have shown that MI results in denervation of infarct regions and induces diffuse nerve sprouting over the peri-infarct and infarct regions. Failure of the sprouting nerve terminals to form mature synapses might contribute to the functional denervation and thus result in reduced re-uptake of norepinephrine at the pre-synaptic cleft to cause myocardial norepinephrine spillover. These changes in the regional sympathetic innervation can contribute to myocardial dysfunction by impairing the inotropic response to norepinephrine. Indeed, clinical studies have demonstrated that regional sympathetic denervation is associated with impaired regional LV function. In this study, we have demonstrated that 10 weeks of either intermittent or continuous SCS induces significant remodelling of sympathetic nerve sprouting and re-innervation of the myocardium. In contrast to the control group, SCS-treated animals showed diffuse and more homogenous sympathetic nerve sprouting and sympathetic re-innervation over the infarct and peri-infarct regions. This remodelling of sympathetic innervation is associated with reduced myocardial norepinephrine spillover and increased expression of myocardial norepinephrine receptors. Previous studies showed that nerve denervation reduces the expression of SERCA-2a that may contribute to LV dysfunction. SERCA is a downstream target for the activation of β-adrenergic receptors and its decreased expression is associated with dysfunction of cardiomyocytes. We observed an increased expression of SERCA-2a at the normal, peri-infarct, and infarct regions in the SCS-treated animals. Therefore, an increased expression of SERCA-2a via induction of sympathetic re-innervation is a potential mechanism that contributes to improvement in LV function by chronic SCS. Interestingly, clinical studies suggest that sympathetic re-innervation as determined by the 123I-MIBG scan and increased expression of SERCA after cardiac resynchronization therapy are associated with an improved clinical response and LV function, suggesting that a similar mechanism to SCS might operate in cardiac resynchronization therapy to improve LV function in HF. Alternatively, in contrast to cardiac resynchronization that has been shown to be effective in HF with wide QRS duration, SCS is potentially applicable to HF independent of the QRS duration.

This study has some limitations. First, it remains unclear whether the beneficial effects of SCS on the remodelling of sympathetic innervation and LV function persist after cessation of SCS. Second, the effect of SCS on the occurrence of spontaneous VT was not studied as we did not observe any spontaneous VT or sudden death following induction of MI and HF in our porcine animal. While prior canine studies suggest that SCS reduces the incidence of VT, the potential long-term pro-arrhythmic effect of sympathetic re-innervation needs to be addressed in future studies. Third, the relative contribution of modulation of the parasympathetic vs. sympathetic nervous system to the beneficial effect of SCS in ischaemic HF was not studied. Fourth, direct nerve recording of activity at the stellate ganglia or the cardiac nerve plexus after SCS was not performed. Fifth, detailed histological assessment of LV remodelling after SCS was not performed in this study. Finally, the long-term safety and therapeutic efficacy of chronic SCS will be addressed by ongoing pilot human trials: The SCS HEART (Spinal cord stimulation for Heart Failure, NCT01362275); DEFEAT-HF study (Determining the Feasibility of spinal cord neuromodulation for the treatment of chronic HF, NCT01112579); and TAME-HF (Trial of autonomic neuromodulation for treatment of chronic HF, NCT01820130).

Supplementary material

Supplementary material is available at Europace online.

Funding

This study was supported in part by the Center for Innovation and Strategic Collaboration (CISC) Division, St Jude Medical, Inc., USA and the Research Grants Council of Hong Kong, General Research Fund (No. HKU 7801/10M, HKU 7811/11M).

Conflict of interest: C.S. and P.C. are employees of CISC Division, St Jude Medical, Inc., USA; and H.-F.T. received an honorarium and research grant from the CISC Division, St Jude Medical, Inc., USA.
References


