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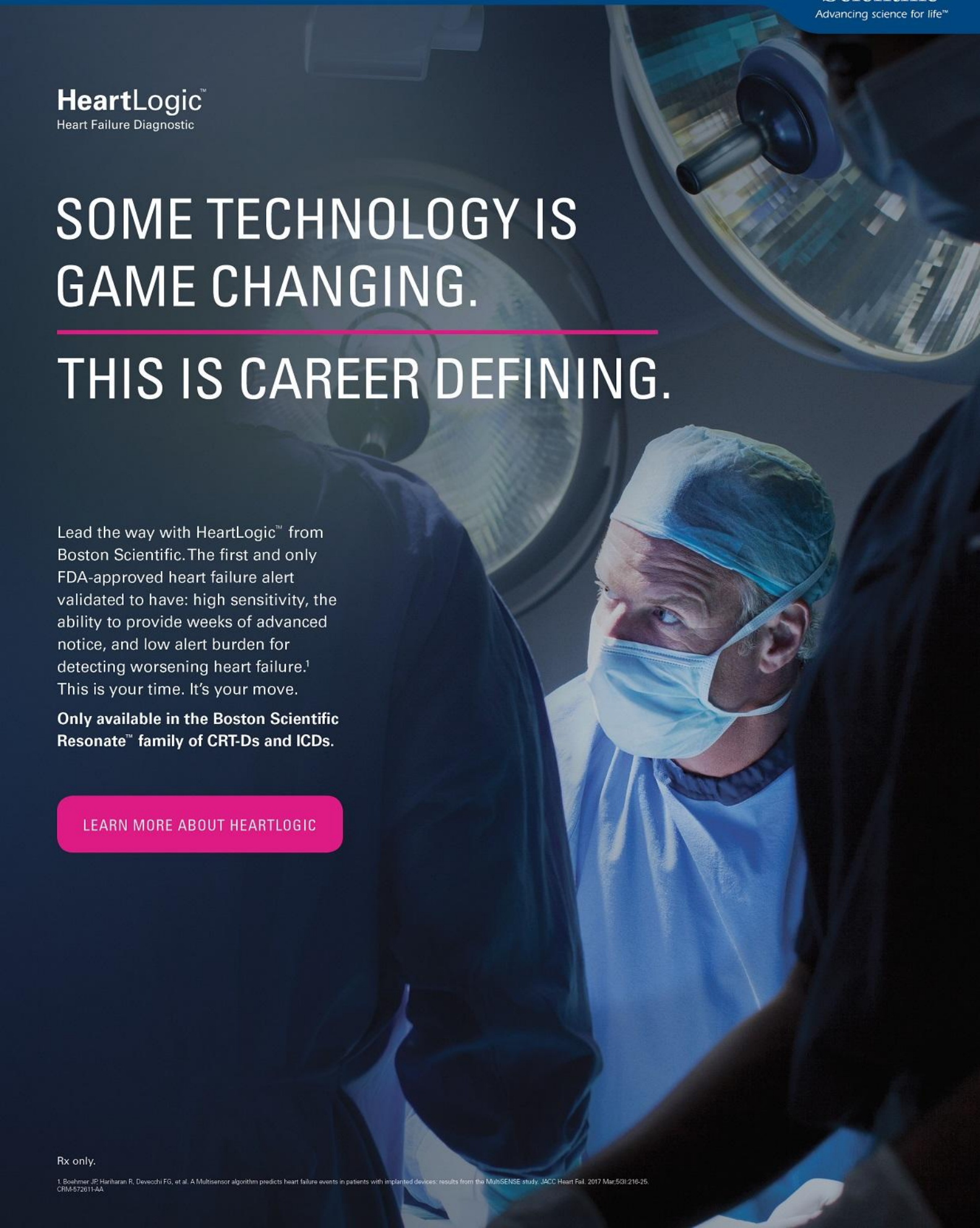

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Thoracic Spinal Cord Stimulation Improves Cardiac Contractile Function and Myocardial Oxygen Consumption in a Porcine Model of Ischemic Heart Failure

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Thoracic Spinal Cord Stimulation. ***Background:*** **Prior experimental studies show that thoracic spinal cord stimulation (SCS) improves left ventricular (LV) ejection fraction (LVEF). The mechanism of this improvement in the LV contractile function after SCS and its effects on the myocardial oxygen consumption remains unknown.**

Methods and Results: **We performed thoracic SCS (T1-T2 level) followed by 4 weeks of rapid ventricular pacing in 9 adult pigs with ischemic heart failure (HF) induced by myocardial infarction (MI). At 24 hours off-pacing, detailed echocardiogram and invasive hemodynamic assessment were performed to determine LV contractile function and myocardial oxygen consumption. Serum norepinephrine level was measured before and after SCS. SCS was performed on 2 occasions for 15 minutes, 30 minutes apart (recovery) with 50 Hz frequency (pulse width 0.2 millisecond, 90% of motor threshold at 2 Hz output). Echocardiogram revealed significant decrease in LVEF (33.8 ± 1.8% vs 66.5 ± 1.7%, $P < 0.01$) after induction of MI and HF. Compared with MI and HF, acute SCS significantly increased LVEF and +dP/dt (all $P < 0.05$). Withdrawal of SCS during recovery decreased +dP/dt, but not LVEF that increased again with repeated SCS. Myocardial oxygen consumption also significantly decreased during SCS compared with MI and HF ($P = 0.006$) without any change in serum norepinephrine level ($P = 0.9$). Speckle tracking imaging showed significant improvement in global and regional circumferential strains over the infarcted mid and apical regions, decreased in time to peak circumferential strain over the lateral and posterior wall after SCS, and the degree of intraventricular dyssynchrony during SCS compared with MI and HF ($P < 0.05$).**

Conclusions: **In a porcine model of ischemic HF, acute SCS improved global and regional LV contractile function and intraventricular dyssynchrony, and decreased myocardial oxygen consumption without elevation of norepinephrine level.** *(J Cardiovasc Electrophysiol, Vol. 23, pp. 534-540, May 2012)*

heart failure, ischemic cardiomyopathy, myocardial infarction, pacing, spinal cord stimulation

Introduction

Despite recent advances in reperfusion therapy for acute myocardial infarction (MI) and pharmacotherapy for post-MI left ventricular (LV) remodeling, the incidence and mortality of post-MI heart failure (HF) are increasing.[1,2] About 30% of patients develop intractable HF after acute MI.[3,4] It is estimated that there are globally more than 15 million patients with HF. This has become a major clinical and public health challenge because of the aging population. There is, thus, tremendous interest in the discovery of novel therapies for post-MI LV remodeling and dysfunction.

Sympathetic–parasympathetic interaction plays a critical role in the physiological and pathophysiological control of the heart. In HF, dysregulation of the autonomic nervous system with increased sympathetic tone and decreased parasympathetic tone are observed. This imbalance is associated with progression of HF and increased mortality.[5,6] Although suppression of the sympathetic nervous system with β-blockers alone has reduced HF mortality by up to 35%,[7] a significant proportion of patients with HF are intolerant to such therapy.[8] No pharmacological therapy can directly enhance the parasympathetic nervous system.[9] Thus, a novel therapeutic approach that modulates the autonomic nervous system to restore this imbalance between the sympathetic and parasympathetic nervous system may improve symptoms and/or clinical outcome.

Spinal cord stimulation (SCS) with an implantable device has been used clinically to relieve symptoms in patients

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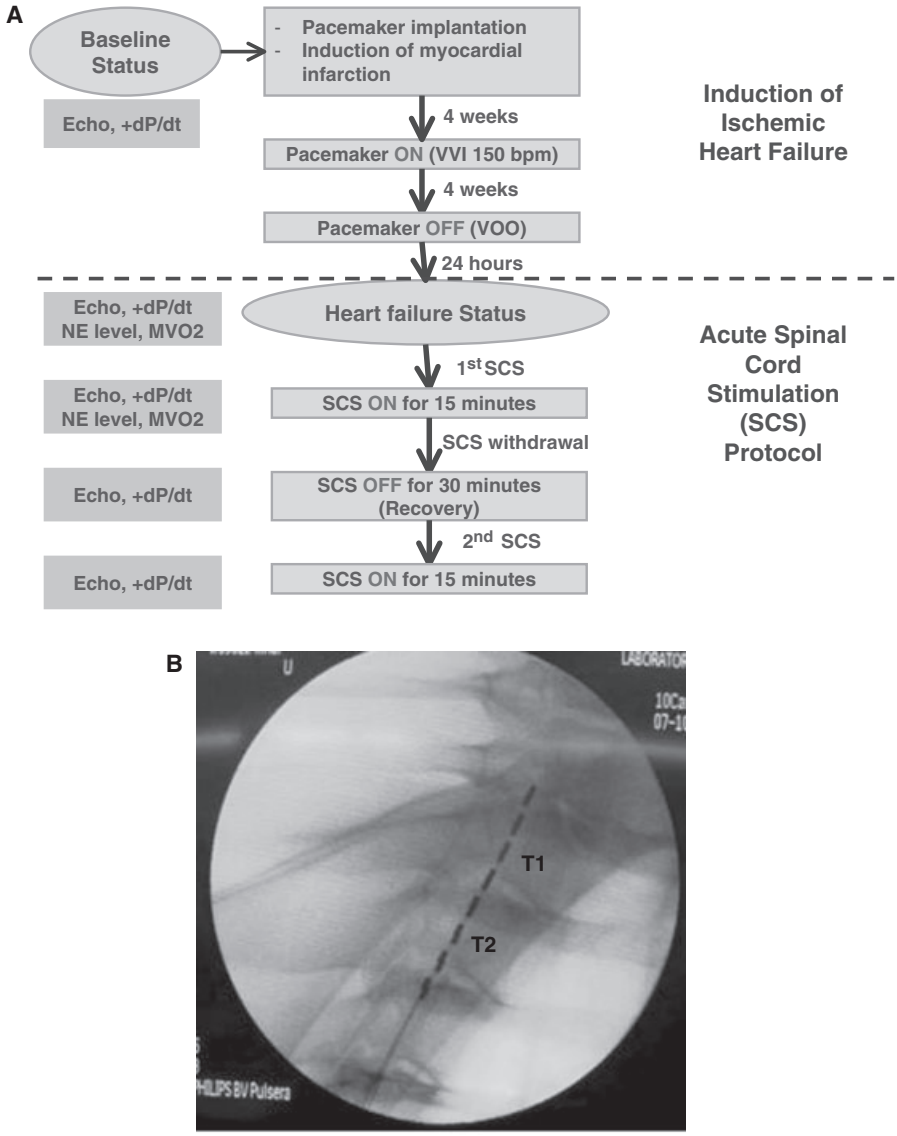

Figure 1. *A: Flow-chart of the study protocol. B: Lateral view of the fluoroscopic image to show the location of the octrode lead at the T1-T2 level.*

with refractory angina and chronic pain syndrome.[10,11] Although the mechanisms by which SCS exerts its effects remain unclear, prior studies have suggested that thoracic SCS suppresses peripheral sympathetic tone by modulation of the intrinsic afferent sensory cardiac neurons related to sympathetic excitation.[12–14] In addition, SCS enhances parasympathetic tone as reflected by a slowing of the sinus rate and prolongation of atrioventricular nodal conduction time and the ventricular refractory period.[15] SCS may, thus, offer a novel therapeutic approach that can restore this imbalance between the sympathetic and parasympathetic nervous system in HF.

In a canine model of post-MI HF, short-term thoracic SCS reduced the incidence of ventricular tachyarrhythmias (VT) induced by acute myocardial ischemia[16]; chronic thoracic SCS further improved the LV ejection fraction (LVEF) beyond conventional medical therapy with angiotensin converting enzyme inhibitor (ACEI) and β-blocker.[17] Nevertheless, the mechanism by which SCS improves LV contractile function is unknown. It is also unclear whether increased LV contractile function with acute thoracic SCS is associated with increased myocardial oxygen consumption that may subsequently lead to further worsening of LV function and HF progression. The aim of this study was to investigate the effect of acute SCS on LV contractile function using invasive hemodynamic assessment and detailed noninvasive echocardiographic measurements, including strain and strain rate imaging, in a porcine model of ischemic HF.

Methods

Animal Model of Post-MI HF

Female pigs weighing between 35 and 45 kg (9–12 months old) were used for this study. Acute MI was induced in all animals by coronary artery embolization as described previously.[18,19] In brief, all animals were anesthetized with tiletamine and zolezepam (Zoletil 20 mg/kg intramuscularly). Endotracheal intubation was performed and anesthesia maintained with a propofol infusion and oxygen while the animals were mechanically ventilated. After initial coronary angiography, the left circumflex coronary artery distal to the first oblique margin branch was occluded with balloon inflation and 700 μm microspheres were injected to generate MI. The

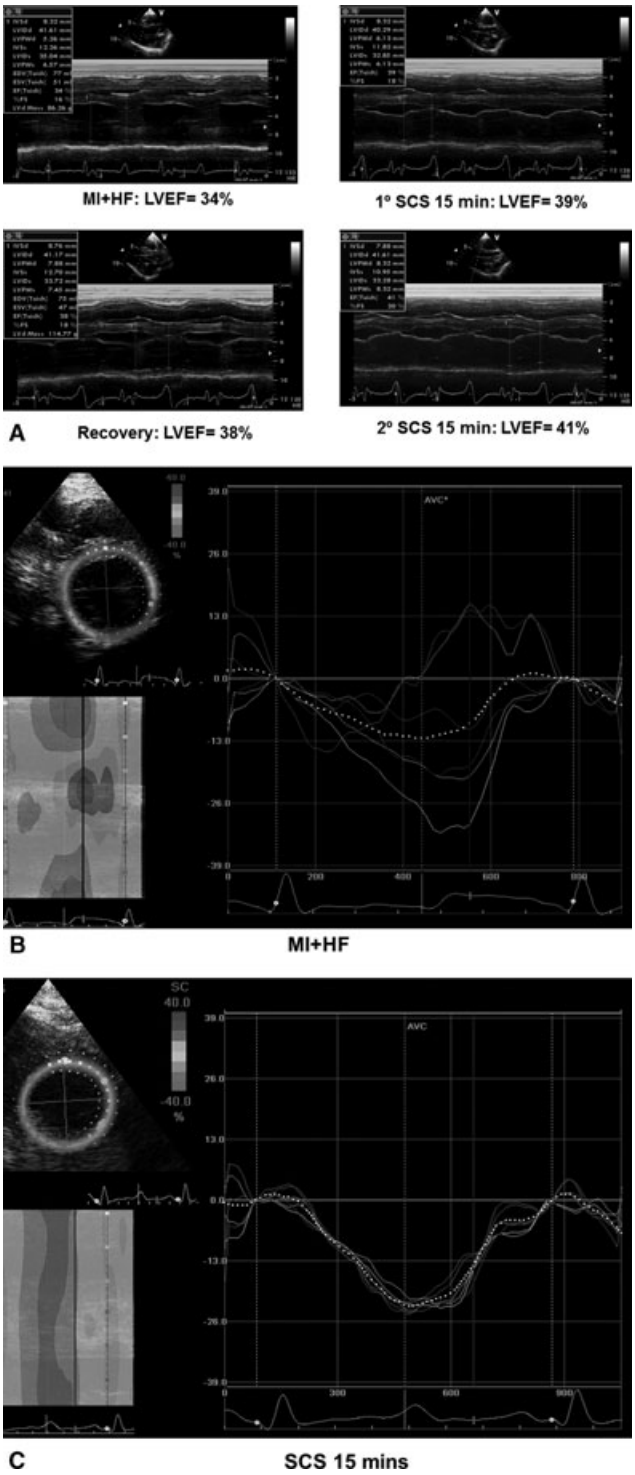

Figure 2. *A: Examples of M-mode echocardiographic images to show the measurement of left ventricular ejection fraction (LVEF) in an animal with myocardial infarction and heart failure (MI and HF) before and during repeated spinal cord stimulation (SCS). B: Speckle tracking images in an animal with MI and HF before SCS. C: Speckle tracking images in an animal with MI and HF during SCS.*

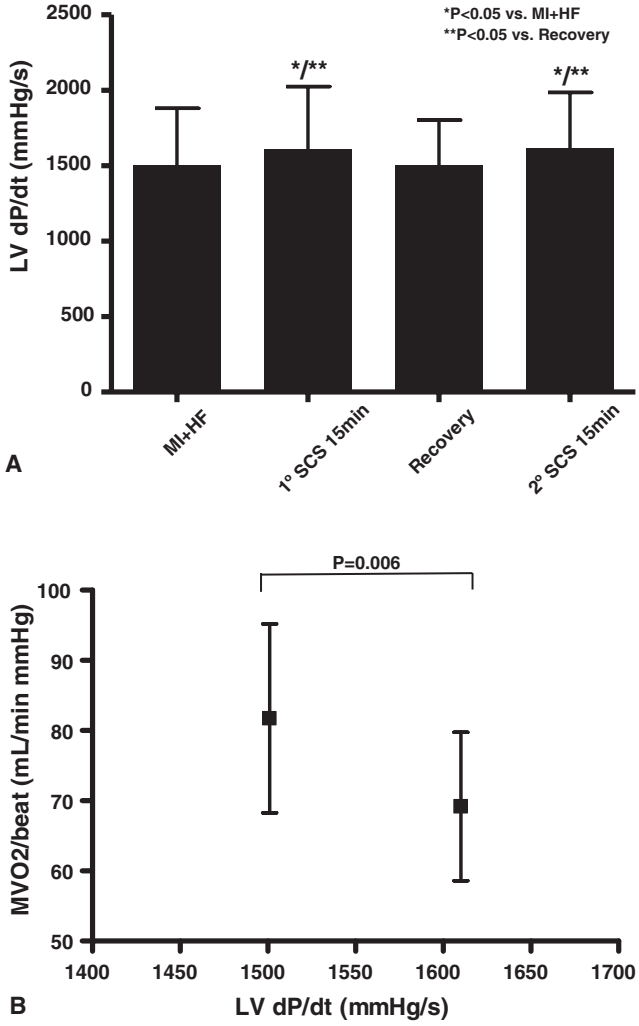

Figure 3. *A: Serial measurement of left ventricular (LV) +dP/dt in animals with myocardial infarction and heart failure (MI and HF) before and during repeated spinal cord stimulation (SCS). B: Myocardial oxygen consumption (MVO2) in animals with MI and HF before and during SCS.*

on-line LV pressure–volume loop as measured by invasive hemodynamic assessment and transthoracic echocardiogram were performed during the procedure to ensure at least 30% reduction in LVEF and dP/dt. Intravenous amiodarone (150 mg), heparin (10,000 IU), and lidocaine (50 mg) were given during the procedure. In case of sustained VT, external cardioversion was performed immediately.

Using a sterile surgical technique, all animals underwent implantation of a single chamber pacemaker following induction of MI. In brief, an active fixation pacing lead was placed under fluoroscopic guidance through the right internal jugular vein into the right ventricular apex. This was connected to a pacemaker and the system was subsequently implanted in the neck region. The device was programmed to VVI mode (35 bpm; output at 2 times diastolic threshold; pulse duration of 0.5 milliseconds except during high-rate pacing at 150 bpm). A 12-lead ECG, oxygen saturation, arterial blood pressure, and transthoracic echocardiogram were performed during the procedure. All animal experiments were conformed to 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.

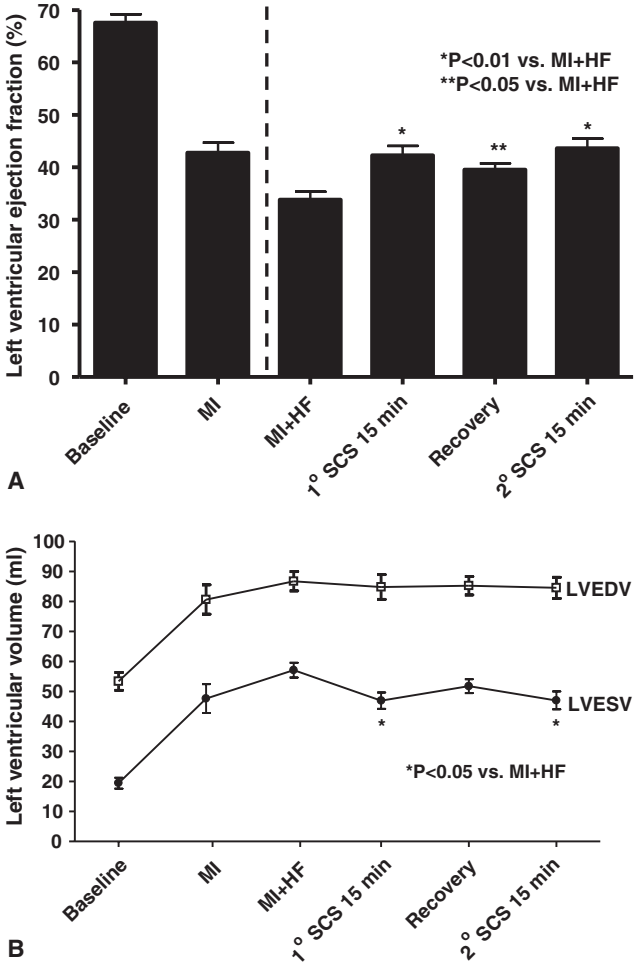

Figure 4. *A: Serial measurements of left ventricular ejection fraction (LVEF) in animals with myocardial infarction and heart failure (MI and HF) before and during repeated spinal cord stimulation (SCS). B: Serial measurements of left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) in animals with MI and HF before and during repeated SCS.*

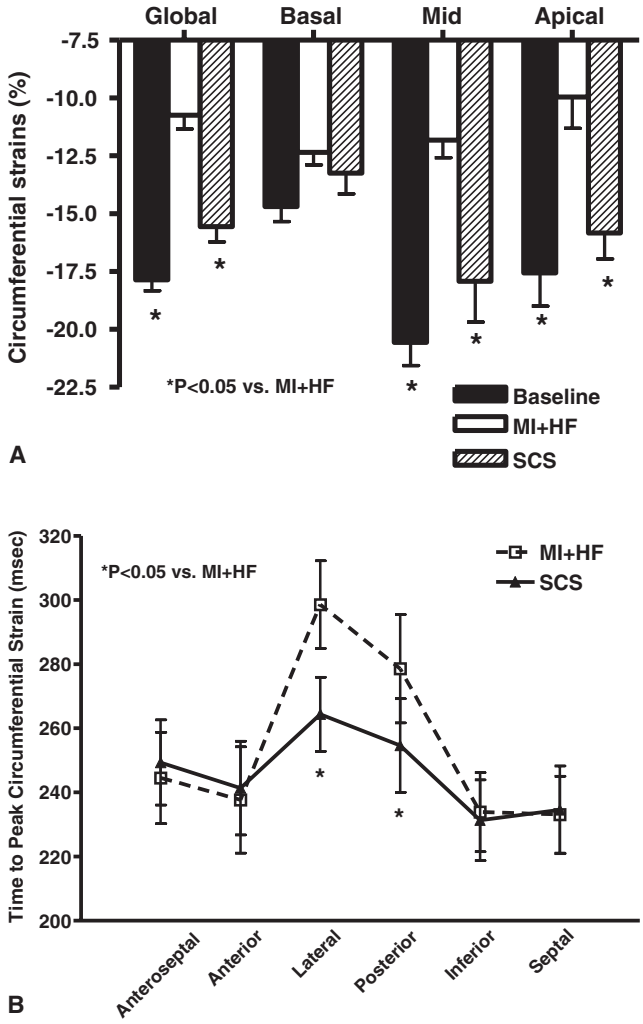

Figure 5. *A: Measurements of global and regional left ventricular circumferential strains in animals before (baseline) and after myocardial infarction and heart failure (MI and HF), and after spinal cord stimulation (SCS). B: Measurements of time-to-peak circumferential strains over anteroseptal, anterior, lateral, posterior, inferior and septal region in animals with MI and HF before and after SCS.*

Study Protocol

At 4 weeks following induction of MI, animals with LVEF <45% on echocardiogram underwent a further 4 weeks of rapid ventricular pacing (150 bpm) for induction of HF. After ventricular pacing was turned off for 24 hours, echocardiographic and invasive hemodynamic assessments were performed to determine the LV contractile function and myocardial oxygen consumption before and during short-term SCS. Following baseline measurements (hemodynamics, ECG and echocardiographic parameters), 15 minutes of SCS at the 1st and 2nd thoracic level (T1-T2) was applied with 50 Hz of frequency, pulse width of 0.2 milliseconds, and the same 90% of motor threshold as determined by a 2 Hz output. Hemodynamic and ECG measurements were recorded every 5 minutes and echocardiogram was performed before the end of 15 minutes SCS. Blood samples were taken to assess serum B-type natriuretic peptide level and norepinephrine levels; coronary blood flow and oxygen saturation measurements were taken to calculate myocardial oxygen consumption. After 30 minutes of recovery period following the SCS, repeat hemodynamic, ECG and echocardiographic parameters were obtained. Then SCS at T1–T2 was repeated for another 15 minutes and measurement of different variables were repeated to determine the acute "ON" and "OFF" effects of SCS on cardiac performance (Fig. 1A).

Invasive hemodynamic assessment

Detailed invasive hemodynamic measurement was performed during induction of MI and 8 weeks post-MI to assess changes in LV function before and after SCS.[19] In brief, a 7-Fr combined catheter-micromanometer (Millar Instruments, Houston, TX, USA) was advanced into the carotid artery to obtain peripheral blood pressure estimation and then advanced into the LV for measurement of LV +dP/dt.

For measurement of myocardial oxygen consumption before and during acute SCS, an intracoronary Doppler catheter (Volcano, Rancho Cordova, CA, USA) was placed in the proximal left main coronary artery to monitor coronary flow, digitizing the analog-output signal for analysis as described.[20] Changes in catheter position and vessel diameters

before and during SCS were determined by contrast imaging. The flow velocity was presumed to be proportional to volume flow. The arterial-coronary sinus oxygen saturation difference (ΔAVO_2) was determined by i-STAT (Abbott Point of Care Inc., Princeton, NJ, USA) point-of care machine.

Echocardiographic measurements

Standard transthoracic echocardiogram including 2D, M-mode, Doppler and tissue Doppler imaging was performed using a commercially available echocardiographic system (Vivid i, GE Vingmed, Horten, Norway) equipped with a 3–9 MHz transducer. In each animal, standard 2D and M-mode echocardiography were performed to measure LV ejection fraction and LV end-diastolic and end-systolic diameters[21] (Fig. 2A). Tissue Doppler images were recorded at the short axis view only because of the limited echo window in animals to analyze global and regional circumferential strains (Fig. 2B-C).[22] All echocardiographic measurements were interpreted off-line in a blinded fashion using a computer workstation (GE Medical, EchoPac, Horten, Norway).

SCS implant

The animals were laid in a left lateral position following induction of anesthesia. A 14-gauge epidural needle was used to access the epidural space at T10 to L2 level. An octrode percutaneous lead (St. Jude Medical, Plano, TX, USA) with straight removable stylet was introduced to the T1-T2 level under fluoroscopic guidance (Fig. 1B). The lead extender was attached to the stimulator and the lead stimulation threshold tested by obtaining muscle thresholds for both polarities. Stimulation pulses were initiated at 2 Hz, 0.2 milliseconds, gradually increasing the amplitude to observe shoulder motion and muscle twitching. Stimulation threshold was chosen as the lowest output required for a muscle response (range: 0.1–10 mA). Acute SCS was performed at 90% of this motor threshold at 50 Hz and pulse width 0.2 milliseconds.

Biomarkers and histology assessment

Serum samples were tested for porcine norepinephrine with ELISA (Rocky Mountain Diagnostics, Boulder, CO, USA) to assess overall sympathetic activation.

After euthanasia, the heart was cut into 8 sections (7–10 mm thick) perpendicular to the apical-basal axis. The sections of the LV were traced and color photographs of each section were obtained to serve as a permanent record. Planimetry of the tracings was performed to measure the size of infarction (as a percentage of the LV mass).[19]

Statistics

All data are expressed as mean ± SEM. Analyses utilized SPSS software (SPSS Inc., Chicago, IL, USA). Comparisons between parameters before and after SCS were made using Student's *t*-test. Serial changes in echocardiographic and invasive LV hemodynamic data at different time points were compared by one-way repeated analysis of variance with Tukey's test. Statistical significance was defined at a value of $P < 0.05$.

Results

Thirteen pigs with documented MI and impaired LVEF on echocardiogram underwent rapid ventricular pacing to induce HF. 4 of these animals died within 4 weeks of induction of HF, thus 9 animals survived after induction of MI and HF were studied. After pacing was turned off for 24 hours, echocardiogram showed that LVEF decreased from 66.5 ± 1.7% at baseline to 33.8 ± 1.8% with induction of MI and HF ($P < 0.001$), to confirm the establishment of an animal model of HF. Histological examination showed the percentage area of infarct size was 14.8 ± 1.7%.

Compared with MI and HF, 15 minutes of acute SCS (1st SCS) significantly increased LV contractile function as determined by +dP/dt (1501 ± 126 mmHg/s vs 1610 ± 138 mmHg/s; $P < 0.05$). Withdrawal of SCS for 30 minutes (recovery period) decreased +dP/dt to MI and HF status (1504 ± 99 mmHg/s) but increased again with repeated SCS (2nd SCS: 1614 ± 131 mmHg/s $P < 0.05$; Ref. Fig. 3A). Doppler assessment revealed no significant changes in coronary blood flow over the left main artery before and after SCS (14.4 ± 2.9 mL/min vs 13.1 ± 2.6 mL/min; $P = 0.09$). Nevertheless, there was a significant decrease in myocardial oxygen consumption following SCS compared with MI and HF status (Fig. 3B; $P = 0.006$). There was no significant change in serum norepinephrine level before and after SCS (314 ± 4.7 pg/mL vs 313 ± 3.1 pg/mL; $P = 0.90$). Furthermore, continuous electrocardiographic monitoring during the SCS protocol did not reveal any significant spontaneous ventricular arrhythmias (>3 beats) before or during SCS.

Detailed echocardiogram examination, including speckle tracking, was performed in all animals. After 15 minutes of SCS (1st SCS), the LVEF significantly increased to 42.3 ± 1.8% compared with MI and HF ($P < 0.01$; Fig. 4A). After withdrawal of SCS for 30 minutes (recovery period), LVEF (39.5 ± 1.2%, $P < 0.05$) remained significantly higher than that of MI and HF, but was insignificantly lower than the LVEF during 1st SCS. Resumption of SCS (2nd SCS) increased LVEF again (43.6 ± 1.8%, Fig. 4A; $P < 0.01$ vs MI and HF), and was similar to the level during 1st SCS ($P > 0.5$, Fig. 4A). Although there were no changes in LV end-diastolic volume, LV end-systolic volume was significantly decreased during SCS compared with that levels associated with MI and HF (Fig. 4B; all $P < 0.05$).

Speckle tracking imaging showed significant improvement in global and regional circumferential strains over the infarcted mid and apical regions during SCS compared with those of MI and HF (Fig. 5A; all $P < 0.05$). There was also a significant decrease in time to peak circumferential strain over the lateral and posterior wall during SCS compared with values for MI and HF (Fig. 5B; all $P < 0.05$). The degree of intraventricular dyssynchrony as measured by the standard derivation of the time to peak circumferential strain was also significantly decreased during SCS as compared with those of MI and HF (126 ± 11 milliseconds vs 165 ± 8 milliseconds; $P < 0.05$; Ref. Fig. 2B and C).

Discussion

In a porcine model of ischemic HF induced by MI and rapid ventricular pacing, acute SCS improved global and regional LV contractile function as measured by invasive hemodynamic assessment and detailed echocardiographic examination. In this study, short-term SCS resulted in acute improvement in LV +dP/dt and the effect subsided following withdrawal of SCS. Similarly, LVEF increased after short-term SCS. There was nonetheless some residual effect of SCS

on LVEF as levels did not return to those associated with MI and HF after withdrawal of SCS. Speckle tracking imaging showed that SCS improved global and regional contractile function over the infarcted regions, and improved intraventricular dyssynchrony. These improvements in LV contractile function were associated with decreased myocardial oxygen consumption without elevation of the serum norepinephrine level.

Dysregulation of the autonomic nervous system with increased sympathetic tone and decreased parasympathetic tone has been well documented in the presence of HF, and is proposed to play an important role in arrhythmogenesis[23] and progression of HF.[5,6] Activation of the parasympathetic nervous system and inhibition of the sympathetic nervous system with SCS, thus, offers a potential novel therapeutic approach to prevent arrhythmias and progressive LV dysfunction in ischemic HF. In a canine model of ischemic HF, Issa *et al.*[16] demonstrated that short-term thoracic SCS reduced the incidence of VT induced by acute myocardial ischemia. Subsequently, Lopshire *et al.*[17] confirmed that long-term SCS also reduced the incidence of spontaneous and ischemic-induced VT in the same animal model of ischemic HF. Odenstedt *et al.*[24] also showed recently that SCS decreased spontaneous VT in a porcine model of ischemia reperfusion. These findings suggest that thoracic SCS has an antiarrhythmic effect on ischemic VT. Interestingly, chronic thoracic SCS also improved LVEF over and above the benefit of current contemporary HF therapy with ACEI and β-blockers.[17] Consistent with this finding, our results demonstrated that short-term SCS significantly improved LV contractile function and LVEF in a porcine model of ischemic HF. Speckle tracking imaging showed that SCS increased global and regional contraction over the infarcted region changes, and improved intraventricular dyssynchrony.

SCS has been approved for the treatment of drug-refractory angina in patients with severe coronary artery disease.[10-12] A recent metaanalysis demonstrated that SCS improves angina symptoms and functional status in refractory angina patients.[25] The antiischemic effect of SCS nonetheless remains unclear. Prior human studies have shown that SCS in patients with refractory angina is associated with decreased myocardial oxygen consumption[13] but no significant change in regional myocardial perfusion as measured by positron emission tomography.[26] As shown in this study, the improvement in LV contractile function with acute SCS in ischemic HF was associated with decreased myocardial oxygen consumption without any change in coronary blood flow. Mechanisms other than changes in coronary blood flow are thus responsible for this improved myocardial performance with decreased myocardial oxygen consumption during SCS. During myocardial ischemia, regionally stunned myocardium contributed to ventricular dyssynchrony.[27] Our results suggest that increased regional contractile function over the infarcted regions decreased intraventricular dyssynchrony, presumably because of improved contraction of the stunned myocardium at the periinfarct regions during SCS. This may account for the improvement in LV function and reduced myocardial oxygen consumption as beneficial effects of cardiac resynchronization therapy observed in HF patients with ventricular dyssynchrony.[20] We also observed no increase in serum norepinephrine level after SCS, confirming that improvement in myocardial performance after SCS was not associated with increased overall sympathetic activity.[28] These findings have an important implication for the potential therapeutic application of SCS for ischemic HF—Treatments that improve myocardial function at the expense of increased myocardial oxygen consumption and excessive sympathetic activation can lead to adverse long-term outcomes.[29]

This study has several limitations. First, it remains unclear whether longer period (>24 hours) after cessation of rapid pacing, further recovery of LV function can be observed in this acute study. This issue needs to be addressed with future long-term study with a control arm without SCS. Second, whether the beneficial effects of SCS on LV function are superior to those achieved with current contemporary HF therapy is unknown. Third, the relative contribution of modulation of parasympathetic versus sympathetic nervous system on the beneficial effect of SCS in ischemic HF was not studied. Fourth, although there was some residual effect on LVEF after withdrawal of SCS, the optimal duration of stimulation remains unclear.

Conclusion

In a porcine model of ischemic HF, acute SCS improved LV contractile function and LVEF. These beneficial effects of SCS on myocardial performance seem to be mediated by decreased intraventricular dyssynchrony, and myocardial oxygen consumption without elevation of serum norepinephrine level.

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