Spinal Cord Stimulation Improves Ventricular Function and Reduces Ventricular Arrhythmias in a Canine Postinfarction Heart Failure Model

John C. Lopshire, MD, PhD; Xiaohong Zhou, MD; Cristian Dusa, MD; Takeshi Ueyama, MD; Joshua Rosenberger, MPH; Nicole Courtney, BS; Michael Ujhelyi, PharmD; Thomas Mullen, PhD; Mithilesh Das, MD; Douglas P. Zipes, MD

Background—Spinal cord stimulation (SCS) reduces the incidence of ventricular tachyarrhythmias in experimental models. This study investigated the effects of long-term SCS on ventricular function in a postinfarction canine heart failure model.

Methods and Results—In stage 1, dogs underwent implantable cardioverter-defibrillator implantation and embolization of the left anterior descending artery followed by right ventricular pacing (240 ppm) for 3 weeks to produce heart failure. In stage 2, 28 surviving animals were assigned to the SCS (delivered at the T4/T5 spinal region for 2 hours 3 times a day), medicine (MED; carvedilol therapy at 12.5 mg PO BID), or control (CTRL; no therapy) group for the initial phase 1 study. In a subsequent phase 2 study, 32 stage 1 survivors were equally randomized to the SCS, MEDS (carvedilol plus ramipril 2.5 mg PO QD), SCS plus MEDS (concurrent therapy), or CTRL group. Animals were monitored for 5 weeks (phase 1) or 10 weeks (phase 2). In stage 3, all phase 1 animals underwent circumflex artery balloon occlusion for 1 hour. In the SCS group, left ventricular ejection fraction was 65 ± 5% at baseline, 17 ± 3% at the end of stage 1, and 47 ± 7% at the end of stage 2. In the MED group, left ventricular ejection fraction was 61 ± 4% at baseline, 18 ± 3% at the end of stage 1, and 34 ± 4% at the end of stage 2. In the CTRL group, left ventricular ejection fraction was 64 ± 5% at baseline, 19 ± 5% at the end of stage 1, and 28 ± 3% at the end of stage 2. Left ventricular ejection fraction was significantly improved in the SCS compared with the MED and CTRL groups (P < 0.001 for both). The mean number of spontaneous nonsustained ventricular tachyarrhythmias during stage 2 and the occurrence of ischemic ventricular tachyarrhythmias during stage 3 also were significantly decreased in the SCS (27 ± 17% and 27%, respectively; P < 0.03) and MED (58 ± 42 and 33%; P < 0.05) versus CTRL (88 ± 52 and 76%) group. After 10 weeks in the phase 2 studies, the greatest recovery in ejection fraction was noted in the SCS (52 ± 5%) and MEDS (46 ± 4%) groups compared with the MEDS (38 ± 2%) and CTRL (31 ± 4%) groups.

Conclusion—SCS significantly improved cardiac contractile function and decreased ventricular arrhythmias in canine heart failure. (Circulation. 2009;120:286-294.)

Key Words: arrhythmia ■ death, sudden ■ heart failure ■ nervous system, autonomic ■ tachyarrhythmias

A

lterations in the autonomic nervous system play an important role in the pathophysiology of heart failure (HF) and sudden cardiac death.1,2 Relative increases in sympathetic activation appear to predispose to ventricular arrhythmias, whereas parasympathetic activation and/or sympathetic inhibition seem to be protective.3–6 Accordingly, resetting autonomic tone to favor the parasympathetic nervous system has been attempted to improve symptoms and manifestations of HF and/or to reduce the risk of ventricular arrhythmias. Spinal cord stimulation (SCS) is approved in the United States for the treatment of chronic pain syndromes and has been used to treat intractable angina pectoris.7–11 Although the precise mechanism by which SCS exerts its effects are unknown, current evidence suggests that thoracic SCS decreases sympathetic tone.12,13 Additional studies found that SCS reduces peripheral sympathetic drive induced by right atrial pacing14 and suppresses activity generated by intrinsic afferent sensory cardiac neurons related to sympathetic excitation.15 Moreover, in a canine model, SCS caused vagal-like responses by slowing sinus rate and prolonging atrioventricular nodal conduction time and ventricular refractory period.16 In a canine postinfarction HF model, our laboratory has shown that short-term SCS or intrathecal clonidine perfusion can decrease the incidence of ischemic ventricular
tachyarrhythmias (VTs). These findings suggest that long-term thoracic SCS might improve the manifestations of HF and protect against ventricular arrhythmias. The present study tested the hypothesis that long-term thoracic SCS improves clinical HF parameters and left ventricular function and reduces the occurrence of VTs in a canine model of healed myocardial infarction (MI) and pacing-induced HF.

Clinical Perspective on p 294

Methods

A previously reported canine model of healed MI and pacing-induced HF that has decreased left ventricular systolic function and increased incidence of ventricular arrhythmias was used for these studies. Seventy-five adult male mongrel dogs (initially weighing 25 to 30 kg) were tranquilized with thiopental sodium (15 to 20 mg/kg IV) and ventilated with room air containing 1% to 2% isoflurane. A 12-lead ECG, oxygen saturation, arterial blood pressure, body weight, serum sample, and transthoracic echocardiogram were obtained during all procedures. Sterile surgical techniques were used. In the initial phase 1 and subsequent phase 2 studies, the experimental protocol consisted of 3 stages of surgical procedures (animals were anesthetized during each surgical procedure only) with an intervening 5-week HF induction interval followed by a 5- or 10-week treatment interval (Figure 1). In the first stage, animals underwent implantation of an implantable cardioverter-defibrillator (ICD) followed by creation of MI and subsequent high-rate ventricular pacing to induce HF. In the second stage of the phase 1 studies, 22 surviving animals were equally randomized to either the control condition (CTRL group) or chronic neuromodulation via placement of an implantable SCS system (SCS group). Six additional animals were treated medically with carvedilol (MED group). In the second phase of the stage 2 studies, 32 surviving animals were equally randomized to receive SCS; carvedilol and ramipril (MEDS); current SCS, carvedilol, and ramipril (SCS + MEDS); or no therapy (CTRL). In the final stage, animals underwent induction of myocardial ischemia (phase 1 animals only) and eventual euthanasia (all animals). All procedures adhered to National Institutes of Health guidelines for animal testing and were approved by the Indiana University Institutional Animal Care and Use Committee.

Stage 1: Animal Model Preparation

ICD Implantation

Under fluoroscopic guidance, active fixation pacing or defibrillating leads were placed through the right internal jugular vein into the right atrial appendage or right ventricular apex, respectively. The leads were connected to an ICD (InSync Marquis, Medtronic, Minneapolis, Minn), and the system was subsequently implanted in the neck region. The device was maintained in VVI mode (34 bpm; output at 450 V) just lateral to the right paraspinous area. Monophasic voltage impulses at 2 Hz of 0.2-ms duration were delivered, and threshold was defined as the lowest output required to produce shoulder motion and muscle twitching. Device outputs were then set at 90% of motor threshold (nominally 0.4 to 1.0 V) at 50 Hz with a 0.2-ms pulse duration, and long-term SCS was delivered for 2-hour intervals 3 times daily (onset at midnight, 8 AM, and 4 PM) for 5 to 10 weeks. At 2 and 5 weeks after SCS implantation, repeat SCS threshold testing and fluoroscopic evaluation confirmed stable stimulation thresholds and epidural lead position. Animals assigned to the MEDS group received carvedilol for 5 weeks at a starting oral dose of 3.125 mg twice daily with weekly doubling to a target dose of 12.5 mg twice daily, with average canine weight of 28 kg. This was comparable to clinical dosing at 0.45 mg/kg per dose. Phase 2 animals assigned to the MEDS group received carvedilol at the above regimen plus ramipril 2.5 mg PO daily. The SCS + MEDS group received concurrent SCS and carvedilol/ramipril as described above.

Stage 2: Neurumodulation

A 7F sheath was inserted into the right femoral artery using a modified Seldinger technique. Heparin (2000 U) was administered via intravenous injection. A 6F angiographic catheter (Amplatz-2 or FL-3.5, Boston Scientific, Maple Grove, Minn) was used to engage the left main coronary artery. Baseline angiography was performed during radiocontrast injection (RenO-Dip, Bracco Diagnostics, Irvine, Calif). The catheter was then advanced into the left anterior descending artery just past the first septal branch, and polyvinyl alcohol foam embolization particles (0.2 to 0.3 mL diluted in 10 mL of 1:1 mixture of saline and radiocontrast; Cook Industries, Bloomington, Ind) were injected under fluoroscopic guidance. Repeat angiography was performed to confirm occlusion of the mid and distal segments of the left anterior descending artery. The animal was subsequently monitored for 1 to 2 hours for arrhythmias and hemodynamic instability. MI was confirmed in all animals by the appearance of acute ST-segment and T-wave changes on a surface 12-lead ECGs and new anterior wall motion abnormalities on a transthoracic echocardiogram. After a 2-week recovery period, continuous rapid right ventricular pacing at 240 bpm was initiated and maintained for 3 weeks to induce HF. Rapid pacing was discontinued 1 hour before randomization into stage 2.

Stage 3: Induction of Acute Ischemia

One hour after SCS was discontinued (nominally at 11 AM) in phase 1 animals, percutaneous techniques (described earlier in stage 1) were used to engage a 6F catheter in the left main coronary artery with subsequent angiography. A 4.0×15-mm balloon (Maverick, Boston Scientific) was then advanced into the left circumflex...
Continuous variables were expressed as mean±SD and analyzed with a paired Student t test, 1-way ANOVA, or 2-way repeated-measures ANOVA with a Bonferroni posthoc test. A χ² test was used for qualitative or categorical variables. A value of P<0.05 was considered significant for all tests.

The authors had full access to and take full responsibility for the integrity of the data. All authors contributed to the study and have read and agree to the manuscript as written.

Results

Stage 1: HF Induction Phase

An anterior MI was created in 75 animals. Forty-three (57%) developed acute anterior ST-segment elevation, and 32 (43%) developed ST-segment depression and/or T-wave inversion after left anterior descending artery embolization. Most animals (58 of 75, 77%) demonstrated nonsustained VTs (defined as ≥3 consecutive ventricular beats at a rate of ≥130 bpm with a duration of ≤30 seconds) during the first hour after embolization. Additionally, 21 of 75 animals (28%) developed sustained VTs requiring internal or external defibrillation during this same period. The peri-infarction mortality rate (defined as death resulting from any cause after infarction and before initiation of high-rate pacing) was 20% (15 of 75 animals). In this group, 7 animals died during the initial procedure from complications related to sustained VTs refractory to internal or external defibrillation, and 7 animals died of sustained VTs (confirmed on postmortem review of ICD records) that occurred on postinfarction days 1, 2, 3, 6, and 13. Additionally, 1 animal was euthanized for severe cardiogenic shock on postinfarction day 11. After the 2-week recovery interval, ICD interrogation of the surviving 60 animals revealed increased rates of nonsustained VT (mean,
18±5 events in 14 days; mean duration, 8±3 seconds). These animals subsequently underwent and survived 3 weeks of high-rate right ventricular pacing at 240 ppm. Clinical, electrophysiological, and echocardiographic parameters for the surviving animals from both experimental phases at baseline and after discontinuation of high-rate pacing are shown in the Table. These results are consistent with the induction of HF, as evidenced by significant changes in hemodynamics and serum neurohormone levels, decreased left ventricular systolic function, and the onset of left ventricular dilatation.

Stage 2: Neuromodulation Phase
There was no mortality during this stage. SCS therapy was well tolerated at the defined parameters without complications. Fluoroscopy revealed no significant change in epidural SCS lead position in any of the animals throughout the course of the study. Furthermore, the stimulation threshold was stable across the treatment period, except for 1 animal from the phase 1 study that demonstrated an increase in motor threshold from 0.4 to 0.6 V after 2 weeks of SCS. No crosstalk was apparent between the SCS system and the implanted ICD, as verified by the lack of ICD detections associated with active SCS.

Phase 1 Study: Effect of SCS on Clinical Parameters, Echocardiographic Measures, and Serum Neurohormones
The significant effects of SCS on clinical parameters are provided in Figure 2. The most striking findings were the marked improvement in HF measures in the SCS group. Animals treated with SCS showed significant clinical improvement in blood pressure (Figure 2A and 2B), body weight change from baseline (Figure 2C), and oxygen saturation (Figure 2D). Furthermore, serum B-type natriuretic peptide and norepinephrine levels were decreased to nearly baseline levels after 5 weeks of SCS, as shown in Figure 3. In contrast, MED or CTRL group animals showed less or no significant improvement in the same measures over the 5-week follow-up interval. SCS therapy produced a significant improvement in ejection fraction (Figure 4A). Reversal of left ventricular dilatation also was noted in the SCS group (Figure 4B and 4C). In contrast, MED and CTRL group animals showed less significant regression in chamber dimensions, although they did demonstrate some improvement in left ventricular systolic function at week 5.
Phase 1 Study: Effect of SCS on Spontaneous VTs

The numbers of nonsustained VTs detected by the ICD during the first 2 weeks after embolization, the first 2 weeks of neuromodulation, and the final 3 weeks of neuromodulation for all surviving animals are reported in Figure 5A. The SCS group had significantly fewer nonsustained VT events than CTRL or MED animals. No sustained VTs were detected in animals from any group during stage 2.

Phase 2 Study: Effect of SCS on Clinical Parameters, Echocardiographic Measures, and Serum Neurohormones

The effects of neuromodulation on ambulatory heart rate are shown in Figure 6A. All groups demonstrated increases in heart rate after HF induction. The SCS, SCS+M Edwards, and MEDS groups all demonstrated significant decreases in ambulatory heart rate after 2, 5, and 10 weeks of treatment. Figure 6B shows the effects of neuromodulation on ambulatory blood pressure. All groups demonstrated significant decreases in systolic blood pressure after HF induction. The

SCS and SCS+M Edwards groups demonstrated significant recovery in ambulatory blood pressure after 2, 5, and 10 weeks of treatment compared with the MEDS and CTRL groups. An apparent fold increase in weight was noted after HF induction in all groups, although there was more variation in this parameter than noted in the phase 1 study. The SCS treatment group demonstrated a recovery of body weight to baseline levels after 5 and 10 weeks of therapy (Figure 6C). Oxygen saturation decreased in all groups with HF induction, with recovery of this parameter after treatment in the SCS, SCS+M Edwards, and MEDS groups (Figure 6D). All groups also demonstrated significant decreases in ejection fraction after HF induction, with the SCS and SCS+M Edwards groups demonstrating the most marked recovery of ejection fraction to baseline levels after therapy (Figure 7A). After HF induction, all groups demonstrated significant increases in left ventricular end-diastolic and end-systolic dimensions. However, the SCS and SCS+M Edwards groups demonstrated regression of chamber dimension to baseline levels after 5 and 10 weeks of therapy. Notably, the MEDS group showed no regression of chamber size relative to the CTRL group during the treatment period (Figure 7B and 7C). Serial changes in
serum B-type natriuretic peptide levels and norepinephrine levels were noted after HF induction and subsequent neuromodulation (Figure 8A and 8B). Both markers demonstrated a significant increase after induction of HF. Interestingly, the SCS and SCS+MEDS groups exhibited a greater decline in serum B-type natriuretic peptide levels than the MEDS group. Additionally, these groups also demonstrated very marked early declines in serum norepinephrine levels compared with the MEDS and CTRL groups, and the MEDS group maintained even higher levels of serum norepinephrine than the CTRL group. Finally, the SCS, SCS+MEDS, and MEDS groups had a significantly decreased total number of spontaneous VTs after receiving therapy (20±9 [P=0.01], 55±20 [P=0.01], and 70±27 [P=0.05] events, respectively, 1-way ANOVA) compared with the CTRL group (170±65 events), with the SCS group demonstrating the lowest frequency of VTs during the treatment period.

**Stage 3: Cx Ischemia Phase**

On entry into stage 3, phase 1 animals underwent repeat left main coronary artery angiography, which confirmed the presence of residual left anterior descending artery occlusion. Figure 5B reports the summed incidence of all VTs (nonsustained VT, ventricular tachycardia, and ventricular fibrillation) recorded during circumflex ischemia in stage 3. As shown, fewer animals from the SCS and MEDS groups had events, and those that did have events had fewer total events than the CTRL group. Additionally, the SCS and MED groups demonstrated significantly less ST-segment depression after 10 minutes of ischemia (1.8±0.7 and 1.9±0.6 mm, respectively) compared with the CTRL group (3.7±0.7 mm; P<0.01 for both). At postmortem in the phase 1 animals, the explanted heart had a significantly higher total weight in the CTRL group (321±23 g) compared with the SCS (251±58 g; P=0.001) and MED (292±35 g; P=0.022) groups. Hearts from all groups showed evidence of prior anterior infarct with no significant difference in epicardial scar surface area (21.2±11.1, 20.9±8.1, and 22.6±13 cm²; ANOVA; overall P=0.947) for the CTRL, SCS, and MED groups, respectively.

**Discussion**

**Major Findings**

This study demonstrated in a canine postinfarction HF model that thoracic SCS significantly improved clinical indexes of HF and left ventricular systolic function while decreasing spontaneous and ischemic ventricular arrhythmias.

**Potential Mechanisms**

Some insight into possible actions of SCS in HF and arrhythmia prevention may be gained from clinical observations. The favorable effects of decreasing sympathetic outflow using surgical sympathectomy or pharmacological β-sympathetic blockade to decrease the risk of arrhythmias have been reported for decades.21–23 Interestingly, the routine use of pharmacological sympathetic blockade as a primary treatment of patients with HF emerged only fairly recently. In addition to direct sympatholytic mechanisms, previous work has shown that SCS enhances vagal tone.15,24,25 This may be important because in HF an upregulation of inflammatory signaling occurs,26 and vagal nerve activation has been linked to attenuation of inflammatory responses.27,28 Finally, in other types of experimental canine models, vagal nerve stimulation has decreased the incidence of sudden cardiac death such as in post-MI exercising canines,29 and has improved ventricular function in a canine HF model produced by repeated coronary
embozization.30 Interestingly, an article by Schwartz and coworkers31 has reported a beneficial effect of long-term cervical vagal stimulation in HF patients.

The mechanism(s) in our model by which SCS improved HF and reduced ventricular arrhythmias are likely very complex and theoretically involve changes in and interactions between nervous, cardiac, and endocrine tissues. It seems likely that modulation of autonomic tone—sympatholytic, vagomimetic, or both—played a significant role. The similar effects of SCS and carvedilol on many of the measured parameters and the noted decrease in serum norepinephrine with SCS therapy would tend to support this view. It is important to stress that the benefit of drugs like carvedilol may be that they block both β- and α-adrenergic receptors, which would probably be attained as well by SCS. Blocking α-receptors may be important to prevent some arrhythmias.32 Additional work to elucidate the mechanism(s) of action of SCS in our model is needed. Further insight in this area not only may lead the way for the use of device-based therapies such as SCS in HF and arrhythmia prevention but also may reveal the involvement of discrete cellular signaling pathways and mechanisms that can be targeted via novel pharmacological therapies.

**SCS for Angina**

The use of SCS to treat refractory angina was first reported in 1987.33 Subsequently, many studies have shown that SCS can improve exercise tolerance, decrease the frequency of anginal episodes, improve quality of life, and prolong the time to ECG signs of ischemia.34–37 It does not appear to increase the incidence of ventricular arrhythmias or mask new anginal pain or signs of myocardial ischemia.38 Although the exact mechanisms of these reported antianginal effects have not been described, they probably not only are related to inhibition of pain transmission but also may involve anti-ischemic effects of SCS and the potential mechanisms noted above. In patients with severe angina undergoing ischemic challenge with adenosine, SCS was found to delay the onset of anginal

---

**Figure 7.** Effect of neuromodulation on echocardiographic indexes: phase 2 study. BSLN indicates baseline; After HF, after HF induction; 2 wk, after 2 weeks of neuromodulation stage; 5 wk, after 5 weeks of neuromodulation stage; and 10 wk, after 10 weeks (completion) of neuromodulation stage.*P<0.05 vs group baseline; †P<0.05 vs group after HF induction; ‡P<0.05 vs control group baseline at same time point (2-way repeated-measures ANOVA for all).

**Figure 8.** Effect of neuromodulation on serum neurohormone levels: phase 2 study. BNP indicates B-type natriuretic peptide; BSLN, baseline; After HF, after HF induction; 2 wk, after 2 weeks of neuromodulation stage; 5 wk, after 5 weeks of neuromodulation stage; and 10 wk, after 10 weeks (completion) of neuromodulation stage. *P<0.05 vs group baseline; †P<0.05 vs group after HF induction; ‡P<0.05 vs control group at same time point (2-way repeated-measures ANOVA for all).
pain and to blunt decreases in ejection fraction.\textsuperscript{39} Our work also found decreased ST-segment changes during ischemia in the SCS and MEDs group, suggesting a possible anti-ischemic effect.

**Limitations**
This study evaluated the effects of SCS on ventricular function and ventricular arrhythmias in a canine model with prior MI and superimposed pacing-induced HF. The mechanisms of MI (foam embolization) and HF induction (rapid pacing) in this model are distinctly different from those responsible for cardiac disease in HF patients. This model is an attempt to replicate a clinical condition in patients with coronary artery disease that includes a myocardial scar from an old MI, HF, and angina. As with all animal models, the results of this study need to be confirmed in patients with HF, particularly HF of varied causes. Pacing-induced HF is partially reversible, although the control dogs maintained HF end points during the course of this short-term study. Additionally, the study was partially conducted in anesthetized animals, which might have influenced the results. However, anesthesia was held constant during the study, was conducted in a similar fashion in all experimental groups, and was provided only during the surgical procedures. In addition, the benefits of SCS delivered in awake and mobile animals on left ventricular function and clinical indexes of HF were obviously long-term changes. Moreover, a decrease in non-sustained ventricular arrhythmias was noted in ambulatory animals in this study, suggesting that anesthesia effects alone cannot explain the findings. Studies of longer duration are needed to determine whether the beneficial effects of SCS remain long term.

**Conclusions**
SCS is an emerging therapy for the treatment of patients with severe coronary artery disease, refractory angina, and chronic pain from other causes. The results of the present study indicate that in a canine model with healed MI and HF, thoracic SCS improves clinical indexes of HF and left ventricular systolic function and protects against spontaneous and ischemia-provoked ventricular arrhythmias. These findings suggest that SCS warrants further evaluation in HF patients.

**Sources of Funding**
This work was partially funded by the Herman C. Kranzler Research Fund, the Charles Fisch Research Fund, and Medtronic Inc.

**Disclosures**
This study was partially supported by a research grant from Medtronic Inc, Minneapolis, Minn. Dr Zipes is a consultant to Medtronic and has no equity interests. Drs Zhou, Ujhelyi, and Mullen are full-time Medtronic employees.

**References**


Sudden cardiac arrest and heart failure (HF) are among the leading causes of morbidity and mortality in the industrialized world. The majority of pharmacological therapies available target symptoms or clinical manifestations rather than actually improve cardiac function. Implantable cardioverter-defibrillators and cardiac resynchronization therapy with defibrillation can improve survival but do not markedly improve cardiac function in the majority of patients receiving these therapies, and many patients progress to end-stage HF. At this point, therapeutic options to improve ventricular function include surgical placement of ventricular assist devices or cardiac transplantation. Cardiac transplantation is limited by the static supply of donor organs (currently 2500 to 3000 available per year). Importantly, the cost of these surgical treatments is high, and therefore they can only be offered to a small percentage of the patients who suffer from end-stage HF. This situation underscores the urgent need to develop novel and cost-effective therapies for the treatment of end-stage HF. The present work provides experimental evidence that neuromodulation using spinal cord stimulation (SCS) can significantly improve cardiac function and decrease the prevalence of lethal arrhythmias in a canine infarction and HF model. Because SCS is a less-invasive and morbid therapy than standard surgical options, it may prove to be a novel and effective therapeutic option in the HF patient. Clinical trials are obviously needed to evaluate the safety and efficacy of SCS in human heart failure. If SCS proves to be an effective therapy for human HF, a new treatment paradigm may emerge for this difficult-to-treat patient population.
Spinal Cord Stimulation Improves Ventricular Function and Reduces Ventricular Arrhythmias in a Canine Postinfarction Heart Failure Model

John C. Lopshire, Xiaohong Zhou, Cristian Dusa, Takeshi Ueyama, Joshua Rosenberger, Nicole Courtney, Michael Ujhelyi, Thomas Mullen, Mithilesh Das and Douglas P. Zipes

_Circulation_. 2009;120:286-294; originally published online July 13, 2009;
doi: 10.1161/CIRCULATIONAHA.108.812412

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/120/4/286

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/