Stromal Cell–Derived Factor-1α Is Cardioprotective After Myocardial Infarction

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Background—Heart disease is a leading cause of mortality throughout the world. Tissue damage from vascular occlusive events results in the replacement of contractile myocardium by nonfunctional scar tissue. The potential of new technologies to regenerate damaged myocardium is significant, although cell-based therapies must overcome several technical barriers. One possible cell-independent alternative is the direct administration of small proteins to damaged myocardium.

Methods and Results—Here we show that the secreted signaling protein stromal cell–derived factor-1α (SDF-1α), which activates the cell-survival factor protein kinase B (PKB/Akt) via the G protein–coupled receptor CXCR4, protected tissue after an acute ischemic event in mice and activated Akt within endothelial cells and myocytes of the heart. Significantly better cardiac function than in control mice was evident as early as 24 hours after infarction as well as at 3, 14, and 28 days after infarction. Prolonged survival of hypoxic myocardium was followed by an increase in levels of vascular endothelial growth factor protein and neoangiogenesis. Consistent with improved cardiac function, mice exposed to SDF-1α demonstrated significantly decreased scar formation than control mice.

Conclusion—These findings suggest that SDF-1α may serve a tissue-protective and regenerative role for solid organs suffering a hypoxic insult. (Circulation. 2008;117:2224-2231.)

Key Words: angiogenesis • apoptosis • ischemia • myocardial infarction

Heart disease is the number-one killer of adults in the industrialized world. The majority of acquired heart disease is due to coronary artery disease, in which blood flow to an area of the heart is reduced or eliminated, resulting in death of myocardium and replacement with nonfunctional scar tissue.1,2 Fatal outcomes are common for individuals suffering acute occlusion of a coronary artery, typically within the first 24 hours.

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Hypoxic cardiac tissue after infarction can be divided broadly into 3 distinct zones. The direct area of ischemia that has total loss of blood supply sustains largely irreversible cell death and scar tissue formation. The myocardium immediately surrounding the infarct zone is less severely affected but remains hypoxic. In some cases, cellular changes occur in this area that decrease energy utilization and promote cell survival. This “hibernating myocardium” may eventually recover if neoangiogenesis or redirection of blood flow restores the supply of oxygen and energy substrates.3,4 Finally, the remaining myocardium typically remains well oxygenated and initially free of damage. The expansion of cell death is a key feature of myocardial infarction as partially ischemic regions of the heart ultimately succumb to hypoxia and are replaced by scar tissue.

Efficient methods to limit initial loss of myocardium and subsequent expansion of the infarct in the acute period could be of significant value. In fact, overexpression of the survival kinase Akt (protein kinase B) in mesenchymal stem cells injected into mouse hearts after infarction resulted in a decrease in infarct size,5 possibly as a result of secreted factors from the cells introduced into the heart. Subsequently, work from our laboratory demonstrated that the 43–amino acid protein thymosin β4 activates Akt via integrin linked kinase (ILK) and dramatically protects bordering myocardium from cell death in the first 24 hours after coronary occlusion.6 Given the efficacy of this small protein in our experimental model and the possibility of bypassing hurdles associated with stem cell administration, we investigated the potential for other proteins that activate Akt and have...
angiogenic properties similar to thymosin β4 to provide beneficial effects after infarction. The secreted chemokine stromal cell–derived factor-1α (SDF-1α) and its G protein–coupled receptor CXCR4 have been implicated in cardiogenesis. Signaling downstream of CXCR4 can trigger a chemotactic response resulting in migration toward an increasing SDF-1α gradient.7–10 In addition, in some cell types, CXCR4 signaling can result in activation of Akt and stimulation of cell proliferation, survival, and angiogenesis.11–17

On the basis of these characteristics of SDF-1α and the observation that this chemokine is upregulated after infarction,18 we investigated the potential of SDF-1α to improve cardiac function and damage in murine hearts immediately after coronary occlusion. We found that SDF-1α protected cardiomyocytes from cell death within the first 72 hours after hypoxic insult and also resulted in increased angiogenesis in the area of risk within 72 hours. SDF-1α induced Akt phosphorylation and upregulated vascular endothelial growth factor (VEGF) protein after coronary occlusion in vivo. In vitro, SDF-1α activated Akt in cardiomyocytes and endothelial cells and upregulated VEGF only in endothelial cells. These findings indicate that SDF-1α may affect multiple cell types in vivo to protect and repair the heart.

Methods

Animals and Surgical Procedures

Myocardial infarction was produced in a total of 49 male C57BL/6J mice at 16 weeks of age (weight, 25 to 30 g) by ligation of the left anterior descending coronary artery with an 8-0 Prolene suture, similar to that described.19 The anesthetic agent used was 5% isoflurane with 2.5 L/min O2 for 20 seconds followed by 2% isoflurane and O2. Half were treated with PBS and half with SDF-1α by intracardiac injection. Subsequent echocardiography and other experimental analyses were conducted at various combinations of 1, 3, 14, and 28 days after infarction. Of 49 mice, 45 survived the surgery and PBS/SDF-1α administration. Four mice received both SDF-1α and thymosin β4. For all mice, 2 intracardiac injections were administered into myocardium adjacent to the ischemic zone at the time of ligation. Each injection was 5 µL of 1 of the following in a collagen base: PBS; recombinant (amino acids 22 to 89) mature mouse SDF-1α protein (R&D Systems, Minneapolis, Minn; catalog No. 460-SD-010) at 60 ng/µL; synthetic thymosin β4 at 40 ng/µL; and SDF-1α and thymosin β4 at 60 and 40 ng/µL, respectively.

Analysis of Cardiac Function by Echocardiography

Echocardiograms to assess systolic function were performed with the use of M-mode and 2-dimensional measurements as described19 and were analyzed for fractional shortening (FS) and ejection fraction (EF), respectively. The measurements represented the average of 6 selected cardiac cycles from at least 2 separate scans performed in random-blind fashion with papillary muscles as a point of reference for consistency in level of scan. End diastole was defined as the random-blind fashion with papillary muscles as a point of reference selected cardiac cycles from at least 2 separate scans performed in

Protein Isolation and Analysis

Protein was isolated from homogenized heart tissue with Trizol reagent (Invitrogen, Carlsbad, Calif; catalog No. 15596-018) and standard Invitrogen protocols. The Bradford assay (Bio-Rad Laboratories, Hercules, Calif) was used to quantify protein concentrations. Protein was then used for Western blotting with primary antibodies against ILK, Akt1, Akt-P, VEGF, and GAPDH (all from Santa Cruz Biotechnology, Santa Cruz, Calif).

Primary Cell Culture and Protein Analysis

Ventricular cardiomyocytes were isolated from adult male C57BL/6 mice (weight, 19 to 25 g; Charles River Laboratories, Wilmington, Mass) by collagenase type II (Worthington) dissociation as previously described.20 Human cardiac fibroblasts were purchased from ScienCell Research Laboratories (San Diego, Calif). Human cardiac-derived microvascular endothelial cells (MVECs) were purchased from Lonza (Basel, Switzerland). HL-1 atrial cardiomyocytes were a gift from Dr W.C. Claycomb, Louisiana State University Medical Center. All cell types were serum and growth factor starved for 16 hours and then treated with 500 ng/mL SDF-1α for 30 minutes. Cell lysates were collected for Western blotting with primary antibodies against Akt1 (Santa Cruz Biotechnology) and Akt1/2/3/5-P (Cell Signaling Technology, Danvers, Mass). For VEGF expression analysis, serum-starved MVECs or HL-1 cells were treated with 50 ng/mL of SDF-1α for varying times indicated, and Western blotting was performed with primary antibodies against VEGF and GAPDH (Santa Cruz Biotechnology). All results represent data from at least 3 independent experiments.

Calculation of Scar Circumference

Scar circumference was calculated from 6 trichrome-stained sections through the heart of each mouse with the use of Improvements software (Improvision, Waltham, Mass) in a manner similar to that described.21 Percent circumference of collagen deposition was measured on each section in a blinded fashion and averaged for each mouse. Analyses were done at 42 and 63 days for PBS- or SDF-1α–treated hearts.

Immunohistochemistry

Adult cardiac tissue was processed for immunolabeling experiments by 1 of 3 different methods. Frozen tissue after fixation with 4% paraformaldehyde or 10% formalin followed by 10% and 30% sucrose gradients was used for cryosectioning. Other hearts were embedded in paraffin after fixation in 4% paraformaldehyde or 10% formalin. A third group of hearts was fixed in methyl Carnoy solution (10% glacial acetic acid, 60% methanol, 30% chloroform) followed by 70% ethanol storage until embedding. Adult hearts were sectioned through at least 10 equivalent levels from the base of the heart to the apex. Serial sections were used for trichrome staining and reaction with various antibodies, and cryosections were used for immunofluorescence. Apoptosis in adult hearts was assayed with the DeadEnd Fluorometric TUNEL System (Promega, Madison, Wis; No. G3250), cell proliferation with antibody against phosphohistone H3B (Upstate Biotechnology, Waltham, Mass; No. 06-570), angiogenesis with von Willebrand factor (Dako, Glostrup, Denmark; No. A0082), hematopoietic stem cells with c-kit (Santa Cruz, No. sc-168), and muscle actin with HHF35 (Dako; No. M0635). Paraffin-embedded sections were used for hematoxylin and eosin staining, trichrome staining for scar tissue, and platelet/endothelial cell adhesion molecule staining (BD Biosciences, San Jose, Calif; No. 550274) for angiogenesis. Methyl Carnoy–fixed sections were used for staining with isocitrate B4 (Vector Laboratories, Burlingame, Calif; No. B-1205) for angiogenesis. Quantification for apoptosis and angiogenesis was done by counting the number of cells and vessels, respectively, per high-magnification field of view, with 6 random fields near the area of infarction assayed for each mouse.

Statistical Analyses

Statistical calculations were performed with the use of the t test of variables (2-sample test assuming unequal variances) with 95% CIs.
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
SDF-1α Preserves Cardiac Function After Infarction
To test the hypothesis that SDF-1α protein could improve cardiac function after infarction, we created ligation of the left anterior descending coronary artery in adult male mice to prevent blood flow to a portion of the LV, creating a zone of injury. Injections of PBS or SDF-1α were administered into myocardium at 2 sites near the infarct zone. Mice were then subjected to echocardiography at various time points to measure cardiac function by assessment of FS and EF. All studies and analyses of data were performed in a blinded fashion.

We created myocardial infarctions in adult male mice and treated half with SDF-1α and half with PBS. At 14 days after infarction, LVs of PBS-treated mice had a mean FS of 27.9±1.5% (n=9). SDF-1α treatment resulted in a mean FS of 38.1±1.5% (n=11; P<0.0001). As a second measure of ventricular function, 2-dimensional echocardiographic measurements revealed that the mean fraction of blood ejected from the LV (EF) in PBS-treated mice was 35.0±7.9% compared with a mean of 61.9±3.7% (P<0.0001) in SDF-1α–treated mice (Figure 1A and 1B). At 28 days after infarction, when additional ventricular remodeling has occurred and the scar is typically well formed, we observed a similar trend in cardiac function of SDF-1α–treated mice. FS was 26.8±1.2% (n=9) for the PBS group and 39.2±2.9% (n=11; P<0.0001) for the SDF-1α group, and EF was 31.5±3.5% and 48.8±2.4% (P<0.0001) for PBS and SDF-1α groups, respectively (Figure 1A and 1B). Cardiac function remained depressed relative to sham-operated animals (∼60% FS; ∼75% EF). The improvement at 28 days in FS or EF (46% and 55%, respectively) on SDF-1α treatment corresponded to echocardiographic findings that the EDD and ESD were both significantly smaller in the SDF-1α group, indicating that SDF-1α treatment had resulted in increased cardiac function and decreased cardiac dilation after infarction (Figure 1C). Finally, we found that SDF-1α administration in the absence of infarction did not lead to an increase in cardiac function (data not shown).

Histological analysis revealed a marked reduction in the size of the scar tissue area and therefore a thicker functional anterior wall of the heart on SDF-1α treatment (Figure 2). By 6 weeks after infarction, the ratio of scar tissue circumferential length to LV circumferential length in SDF-1α–treated animals was reduced by 56% from that seen in PBS-treated controls (P<0.001). At 9 weeks after infarction, the reduction of scar circumference in SDF-1α–treated hearts was 43% relative to controls (P<0.001; Figure 2E). The functional improvement persisted in these animals, corresponding to the scar improvement.

The functional and histological improvements observed with the single administration of SDF-1α immediately after coronary ligation suggested that the beneficial effects of SDF-1α may occur in the early stages after infarction. We therefore sought to determine the time frame of functional improvement by performing echocardiography at numerous time points within days of the coronary ligation. Remarkably, as early as 1 day after infarction, we found that FS was 32.2±1.6% (n=8) with PBS treatment compared with 40.2±1.6% (n=8; P<0.0001) with SDF-1α treatment; correspondingly, EF was 40.7±2.7% (n=8) or 56.6±3.7% (n=8; P<0.0001), respectively. This pattern continued 3 days after infarction as SDF-1α–treated mice again demonstrated significant improvement in FS and EF (Figure 1A and 1B).

SDF-1α–mediated functional improvement occurred as early as 24 hours after infarction and continued 3, 14, and 28 days after infarction. We performed parallel experiments with thymosin β4 to investigate the comparative efficacy of SDF-1α and found that improvement of cardiac function after coronary ligation was similar with SDF-1α or thymosin β4. Interestingly, the combination of SDF-1α and thymosin β4...
Cardiac regeneration or repair. Signals arising from stem cells may somehow potentiate this process, but recent studies have suggested that secreted factors play a role. Differentiation of stem cells into functional cardiomyocytes has been in progress for years, but the mechanism by which this occurs to improve function remains unclear. Whether stem cells can actually take up residence and improve cardiac function is still a matter of debate. By 72 hours, however, a highly significant difference was observed with 63.3±16.4 or 1.3±1.5 apoptotic myocytes per field of view in the border myocardium of PBS- or SDF-1α-treated hearts, respectively (P<0.0001; Figure 3K). Thus, bordering myocardium that is normally irreparably damaged after infarction is protected by SDF-1α-directed cell survival.

**SDF-1α Promotes Survival of Ischemic Myocardium**

Our previous data with thymosin β4 suggest that it functions in a cardioprotective fashion within 24 hours after infarction, possibly followed by neoangiogenesis, rather than through recruitment or promotion of stem cell differentiation into cardiomyocytes. However, some reports suggest that SDF-1α can attract CXCR4-expressing hematopoietic stem cells to the heart, where they are assumed to take up residence and improve cardiac function. The mechanism by which the stem cells might improve function remains unclear. Whether stem cells differentiate into functional cardiomyocytes has been in dispute, but recent studies have suggested that secreted signals arising from stem cells may somehow potentiate cardiac regeneration or repair.

To investigate the mechanism by which SDF-1α induces cardiac repair, we examined the degree of cell death in the direct area of infarction and the neighboring area of hypoxic myocardium. Apoptotic cells marked by terminal deoxynucleotidyl transferase–mediated dUTP-biotin nick end labeling (TUNEL) assay were observed in both control and SDF-1α-treated hearts during the first 24 hours and were largely isolated to the border zone located immediately adjacent to the area of infarct (Figure 3A to 3D). However, by 72 hours after infarction, the apoptosis had spread outside of the immediate area of infarction to surrounding myocardial tissue in all directions in the control PBS-treated hearts. In contrast, the SDF-1α–treated hearts showed little or no apoptosis outside of the area of infarct (Figure 3E to 3H). Remote myocardium in both groups remained free of any significant apoptosis at these early time points. Costaining with muscle actin confirmed that cells undergoing apoptosis were indeed myocytes (Figure 3I to 3J). Quantification revealed that at 24 hours after infarction, 84.0±19.6 or 60.7±11.8 apoptotic myocytes per field of view were present in the immediately adjacent border myocardium of PBS- or SDF-1α–treated hearts, respectively; however, this difference was not statistically significant. By 72 hours, however, a highly significant difference was observed with 63.3±16.4 or 1.3±1.5 apoptotic myocytes per field of view in the border myocardium of PBS- or SDF-1α–treated hearts, respectively (P<0.0001; Figure 3K). Thus, bordering myocardium that is normally irreparably damaged after infarction is protected by SDF-1α-directed cell survival.

**SDF-1α Treatment After Myocardial Infarction Results in Increased Angiogenesis**

Although the cardioprotective effects of SDF-1α may aid in survival of hypoxic myocardium, the myocytes ultimately would need to be vascularized to achieve long-term survival. Hence, we investigated the degree of neoangiogenesis in the presence of SDF-1α. An antibody to isoclin B4, a known marker of endothelial cells in the microvasculature, demonstrated a significant increase in the number of capillaries in the area of injury (border zone) in SDF-1α–treated hearts compared with PBS-treated hearts within 72 hours (Figure 4A to 4D). Quantification of the isoclin B4-positive capillaries revealed an ~93% increase in microvasculature over controls (Figure 4E). This observation was validated by increased capillary density that was not observed in unaffected regions of the myocardium. It is difficult to establish, however, whether the increased amount of vasculature bordering the area of infarction is a direct effect of SDF-1α administration, an indirect effect of greater initial cell survival leading to recruitment of new vasculature, or a combination of the two.

**SDF-1α Treatment Increases Akt Phosphorylation and Levels of VEGF Protein**

Our previous observations of ILK and Akt activation on thymosin β4 treatment as well as the known effects of SDF-1α on Akt led us to investigate the response of this pathway in infarcted hearts exposed to SDF-1α. In harvested heart cell lysates from the infarct area, we observed increased levels of ILK protein and increased phosphorylation of its downstream kinase Akt upon SDF-1α treatment, whereas no difference was seen in the amount of total Akt protein. These changes were observed within 24 hours after coronary ligation (data not shown) and were more prominent at 72 hours (Figure 5A). VEGF, a known regulator of angiogenesis, was similarly upregulated at 72 hours in response to SDF-1α,
consistent with the increase in capillary density described in Figure 4.

To determine which cell types are direct targets of SDF-1α treatment, we treated primary cardiac-derived human MVECs, primary human cardiac fibroblasts, a cardiac myocyte cell line (HL-1), and primary adult mouse cardiomyocytes in culture with SDF-1α. We found a modest but reproducible upregulation of phosphorylated Akt in MVECs and cardiomyocytes (HL-1 or primary adult cardiomyocytes) but not in fibroblasts (Figure 5B). These data suggest that SDF-1α may be acting on cardiomyocytes directly but also on endothelial cells that may signal to myocytes in a paracrine fashion. Consistent with this, we found that whereas CXCR4 protein was expressed in all of the cell types examined, it was most highly expressed in MVECs (data not shown). VEGF is one of the putative paracrine factors secreted from endothelial cells that functions in an angiogenic and cardioprotective manner. We observed an upregulation of VEGF protein in response to SDF-1α in MVECs but not in cardiomyocytes. Thus,

Figure 3. SDF-1α promotes cell survival after infarction. TUNEL-positive cells (bright green) in bordering myocardium adjacent to the zone of infarct 24 hours after coronary ligation and PBS (A and B) or SDF-1α (C and D) treatment are shown. TUNEL-positive cells in bordering myocardium were also evident 72 hours after coronary ligation in PBS (E and F) but not SDF-1α (G and H) treatment groups. The right column (I and J) illustrates higher-magnification confocal microscopy of TUNEL-positive cells triple labeled with anti-muscle actin antibody (red striations) to mark cardiomyocytes and DAPI (blue) to mark nuclei. Cardiomyocytes undergoing apoptosis (arrowheads) are present after PBS treatment (I) but absent after SDF-1α treatment (J). Note the reduced DAPI staining in the PBS-treated damaged tissue (I). K, Quantification of myocyte apoptosis from 6 sections per mouse 24 and 72 hours after coronary ligation and administration of PBS or SDF-1α. Bars indicate 95% CIs. *P<0.0001.

Figure 4. SDF-1α treatment induces increased angiogenesis 72 hours after infarction. Immunohistochemistry using isolectin B4 antibody staining to mark endothelial cells demonstrated a higher density of microvasculature in bordering myocardium close to the zone of injury after SDF-1α treatment (C and D) than after PBS treatment (A and B). B and D represent high magnification of A and C, respectively. E, Quantification of vessel density gleaned from 6 sections per mouse 72 hours after coronary ligation and subsequent administration of PBS or SDF-1α. Bars indicate 95% CIs. *P<0.005.
SDF-1α may function in a cardioprotective manner directly on cardiomyocytes and in a paracrine fashion through endothelial cells, in addition to stimulating new recruitment or expansion of the capillary bed.

**Discussion**

In the present report, we propose that SDF-1α, a secreted chemokine that activates Akt, has cell-protective and angiogenic properties under conditions of cardiac tissue hypoxia. After acute myocardial infarction in mice, SDF-1α treatment resulted in decreased cell death and increased angiogenesis within the hypoxic tissue, ultimately leading to reduced scarring and improved cardiac function. Phosphorylation of Akt was increased in vivo, as was upregulation of VEGF in response to SDF-1α, providing potential mechanisms for the observed effects of SDF-1α.

Published reports have alluded to the potential role of SDF-1 in cardiac regeneration and have focused on attraction of bone marrow–derived somatic stem cells to the heart after infarction.22,23 Recent studies, however, have raised considerable doubt about the potential of bone marrow–derived stem cells to transdifferentiate into cardiomyocytes,21,27,28 although they may provide a noncell autonomous benefit via secreted factors that are angiogenic. Whether or not SDF-1α protein alone induces regeneration and thereby improves cardiac function after an acute insult has not been addressed previously, but the notion of SDF-1α–induced recruitment of stem cells into an infarcted tissue has been suspected. Our studies suggest the possibility that SDF-1α may be among the beneficial secreted proteins from noncardiomyocytes that can limit hypoxic damage to the heart.

Our observed short-term improvement data suggest that the initial conservation of function upon SDF-1α treatment is due primarily to preservation of myocardial tissue bordering the immediate area of infarct. This preservation may occur through an Akt-mediated pathway or other SDF-1α–dependent mechanisms. In addition, the observed upregulation of VEGF and the concurrent increase in microvasculature after SDF-1α treatment may be involved in the prolonged recovery of initially protected “hibernating” tissue. Of particular interest is a recent report demonstrating that Akt1 is essential for proper angiogenesis both after ischemia and after VEGF activation,29 lending support to the possibility of SDF-1α–mediated Akt activa-
tion having a direct effect on this process. However, the relative contribution of Akt activation is difficult to discern in vivo and has not been tested here. Given our observed upregulation of VEGF in SDF-1α-treated hearts and in cardiac endothelial cells, it is of interest that VEGF can have a direct effect in promoting cardiomyocyte survival.

Finally, it is also possible that SDF-1α stimulates recruitment of circulating progenitor cells that promote angiogenesis. Thus, long-term cardiac functional improvement may be multifactorial, involving tissue protection and survival, angiogenesis, and progenitor cell recruitment.

In sum, we have presented data that demonstrate a role for SDF-1α in improving cardiac function predominantly by affecting myocyte survival and angiogenesis at an early time point. Future studies will attempt to address the intracellular changes that SDF-1α may be inducing in cardiomyocytes and whether these changes mirror the known metabolic and energy usage adaptations typical of hibernating myocardium.

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Disclosures
Dr Srivastava serves on the scientific advisory board of RegenRx Pharmaceuticals. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

The majority of acquired heart disease is due to coronary artery disease, in which blood flow to an area of the heart is reduced or eliminated, resulting in death of myocardium and replacement with nonfunctional scar tissue. Efficient methods to limit initial loss of myocardium and subsequent expansion of the infarct in the acute period could be of significant value. We investigated the potential of the secreted protein stromal cell–derived factor-1α (SDF-1α) to improve cardiac function and damage in murine hearts immediately after coronary occlusion. We found that SDF-1α protected cardiomyocytes from cell death within the first 72 hours after hypoxic insult and also resulted in increased angiogenesis in the area of risk within 72 hours. SDF-1α induced Akt phosphorylation and upregulated vascular endothelial growth factor protein after coronary occlusion in vivo. In vitro, SDF-1 activated Akt in cardiomyocytes and endothelial cells and upregulated vascular endothelial growth factor only in endothelial cells. These findings indicate that SDF-1α may affect multiple cell types in vivo to protect and repair the heart. Future studies will address the intracellular changes that SDF-1α may be inducing in cardiomyocytes and whether these changes mirror the known metabolic and energy usage adaptations typical of hibernating myocardium.