Effects of Intravenous Levosimendan on Human Coronary Vasomotor Regulation, Left Ventricular Wall Stress, and Myocardial Oxygen Uptake

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Background—Levosimendan is a calcium-sensitizing agent and an inodilator under current investigation in the treatment of decompensated heart failure. The effects of intravenous levosimendan on the human coronary vasculature, together with myocardial wall stress and oxygen uptake, have not been adequately studied.

Methods and Results—Ten adult patients underwent right- and left-heart catheterization. Baseline coronary blood flow was determined with quantitative coronary angiography and an intracoronary Doppler-tipped guidewire. Myocardial oxygen uptake was measured with a coronary sinus catheter. Echocardiography was performed before and 30 minutes after an intravenous infusion of levosimendan (24 μg/kg bolus over 10 minutes) was begun. Pulmonary capillary wedge decreased 37% (P=0.009), cardiac output increased 9% (P=0.04), and systemic vascular resistance decreased 18% (P<0.001). Left ventricular ejection fraction increased 20% (P=0.009), and meridional systolic wall stress decreased 48% (P=0.009). Coronary artery diameter increased 10% at 15 minutes (P=0.001) and 11% at 30 minutes (P=0.01). Coronary artery velocity increased 10% over baseline (P=0.04). Coronary blood flow increased 45% (P=0.02), whereas coronary resistance decreased 36% at 30 minutes (P=0.03). Myocardial oxygen extraction decreased 9% at 30 minutes (P=0.04).

Conclusions—Levosimendan given intravenously exerts vasodilator effects on human coronary conductance and resistance arteries. Despite a decrease in coronary perfusion pressure, coronary blood flow is increased. A reduction in coronary vascular resistance and a decrease in coronary venous oxygen content indicate primary coronary vasodilation by levosimendan. Improved left ventricular systolic function and decreased myocardial oxygen extraction suggest improved myocardial efficiency. (Circulation. 2005;111:1504-1509.)

Key Words: blood flow ■ heart failure ■ hemodynamics ■ inotrope ■ vasodilator agents

Intravenous positive inotropic agents play a central role in the short-term management of patients with decompensated heart failure resulting from left ventricular systolic dysfunction.1,2 The most commonly used positive inotropes, β-adrenergic agonists and phosphodiesterase III/IV inhibitors, exert their positive inotropic effect by increasing cAMP in cardiac myocytes. Although these agents improve hemodynamics rapidly, their use may be limited by several factors.3-5 First, increases in heart rate and the potential for arrhythmogenesis limit dose titration and may result in serious adverse cardiac effects, including myocardial ischemia and arrhythmogenic sudden cardiac death. Second, because of desensitization of the β-adrenergic pathway, severe heart failure patients may have an attenuated benefit from the β-adrenergic agonists.6,7

Calcium-sensitizing agents exert a positive inotropic action by increasing the sensitivity of the myocardial contractile apparatus to calcium.8 These agents do not usually increase the intracellular concentration of cAMP and thus do not have the limitations of causing increased heart rate and stimulation of arrhythmias. Levosimendan is a new myocardial calcium sensitizing agent that binds to troponin C.9,10 Levosimendan has inotropic and vasodilator effects that have been shown to have beneficial short-term hemodynamic and clinical effects in patients with decompensated heart failure.11-13

Animal studies have shown that this agent dilates porcine coronary arteries by opening potassium channels, a relaxation effect that is independent of intracellular free calcium.14 The effects of intravenous levosimendan on the coronary circulation in humans have not been evaluated. We sought to test the hypothesis that levosimendan would lead to coronary vasodilatation. In this study, we examined the human coronary hemodynamic effects of intravenous levosimendan during cardiac catheterization, assessing changes in both the conductance and resistance arteries. We also studied the effects of levosimendan on myocardial oxygen uptake and echocardiography.
graphic measures of left ventricular function and wall stress. By simultaneously measuring changes in left ventricular work, myocardial oxygen uptake, and coronary blood flow, we measured the effects of levosimendan on myocardial mechanical efficiency.

Methods

Study Design and Patient Selection

This was a prospective cohort study that enrolled patients referred for cardiac catheterization and coronary angiography at the University of California–San Francisco Adult Cardiac Catheterization Laboratory. Patients with a contraindication to intravenous hirеп (ie, platelet count <100 000, active or recent bleeding disorder), those with a systolic blood pressure <95 mm Hg, those with heart rate <50 bpm, and those receiving intravenous vasopressors or vasodilators were excluded. Patients with 1 of the following contraindications to systemic vasodilator therapy were excluded: severe stenotic valvular disease, restrictive or obstructive cardiomyopathy, or precapillary pulmonary hypertension. Patients with any of the following contraindications to levosimendan were excluded: severe renal insufficiency (creatinine clearance <30 mL/min), severe hepatic impairment, hypokalemia (serum potassium <3.5 mmol/L), tachycardia (heart rate >100 bpm), and those with a long-QT interval (corrected QT >500 ms) on a 12-lead ECG. Patients without a native coronary artery with <40% diameter stenosis, with prior CABG surgery, and with angiographic evidence of intracoronary thrombus were excluded from the study. Calcium channel blockers and nitrates were withheld ≥24 hours before the study. All patients gave written informed consent before the procedure, and the University of California at San Francisco Committee on Human Research approved the protocol. The number of patients enrolled was prospectively preset at 10.

Study Procedures

Right- and left-heart catheterization and quantitative coronary angiography (QCA) was performed with 6F diagnostic coronary catheters. Transesophageal echocardiography was performed for assessment of left ventricular function. A 6F catheter was inserted into the mid coronary sinus for blood gas measurements. After full heparinization, a 0.014-in Doppler-tipped FloWire (Volcano Therapeutics Inc) was advanced to the mid coronary artery. Levosimendan (Abbott Laboratories; 24 μg/kg IV bolus over 10 minutes) was infused via a peripheral intravenous catheter. Intracoronary Doppler flow was recorded from the same position for 30 minutes after the bolus was started. Repeated QCA was performed at 15 and 30 minutes after the bolus was begun. Repeated coronary sinus blood gas sampling, right-heart catheterization, and echocardiography were performed at 30 minutes.

Echocardiography

Transesophageal echocardiography was performed at baseline and again 30 minutes after the levosimendan infusion was begun (Acuson Sequoia or SONOS 5500, Philips Medical Systems). Echocardiographic contrast (Optison, Amersham; 0.3 to 0.5 mL injected into a peripheral vein) was administered when required to improve endocardial border detection and to enhance Doppler signals. End-diastolic and end-systolic volumes, calculated by use of the biplane method of discs, were then indexed to body surface area. These volumes were used to calculate left ventricular function. Left ventricular meridional systolic wall stress (σa) was calculated as follows: [0.334(P(LVID))/[PWT(1+PWT/LVID)], where P is simultaneous cuff systolic pressure, LVID is end-systolic minor axis dimension, and PWT is end-systolic posterior wall thickness. Left ventricular dP/dt was estimated by measuring the time between 2 points along the mitral regurgitant spectral Doppler profile using the dP/dt mean rate method, as described previously. The E/e′ ratio was calculated as a measure of left ventricular filling pressure, where E is the peak early diastolic mitral inflow velocity (measured with pulsed-wave Doppler) and e′ is the peak early diastolic mitral annular tissue velocity (sample volume placed at the lateral mitral annulus). Echocardiographic data were stored on magneto-optical disks and analyzed offline by a single experienced reader.

QCA Study

The left anterior descending coronary artery was specified prospectively as the preferred coronary artery for QCA, followed by the left circumflex and then the right coronary artery if angiographic exclusion criteria were present. QCA was performed at baseline, 15 minutes, and 30 minutes. Coronary angiographic images were acquired and analyzed digitally with a real-time digital image acquisition and analysis system (General Electric Advantage system with Camtronics Medical Systems digital processing or Philips Allura Xper Flat Detector 10). Unblinded analysis was performed offline after the procedures with the Camtronic ARTREK QCA algorithm. QCA analysis determined the diameter and cross-sectional area of the mid coronary artery 5 mm proximal to the tip of the FloWire in the sample volume site.

Intracoronary Doppler Velocity Protocol

The Doppler guidewire FloWire system has a miniature Doppler ultrasound crystal that transmits signals at a carrier frequency of 15 MHz and receives pulsed-wave ultrasound signals, sampled at a distance of 5 mm from the guidewire tip. The Doppler signals were analyzed by a FloMap instrument (Volcano Therapeutics Inc) in which dedicated digital signal processing chips perform the fast Fourier transformation required for the spectral display. The spectrum and ECG were displayed simultaneously on the monitor. Also displayed were quantitative measurements of average peak velocity (APV) and ratio of diastolic to systolic velocity. The monitor display was continuously recorded on a high-quality super-VHS (S-VHS, Fujif) videotape for subsequent offline unblinded analysis.

Calculations of Systemic Hemodynamics, Coronary Blood Flow Hemodynamics, and Myocardial Oxygen Consumption

Stroke volume index (SVI; mL/m²) was calculated as follows:

SVI = CI/HR, where CI is cardiac index and HR is heart rate.

Coronary blood flow (CBF; mL/min) in the epicardial artery studied was calculated as follows:

CBF = π(D²/4)(APV/2)(0.6).20

Coronary oxygen consumption (CR; mm Hg · min · mL⁻¹) was calculated from the following:

CR = (MAP – RAP)(CO/O₂)(80),

where MAP is mean arterial pressure, RAP is right atrial pressure, and CO is cardiac output. Pulmonary vascular resistance (PVR; Wood units) was determined from the following:

PVR = (PAM – PCWP)/CO, where PAM is pulmonary artery mean pressure.

Coronary blood flow (CBF; mL/min) in the epicardial artery studied was calculated as follows:

CBF = π(D²/4)(APV/2)(0.6).

Coronary oxygen consumption (CR; mm Hg · min · mL⁻¹) was found from the following:

CR = (MAP – RAP)/CBF.

All patients received 2 L/min of nasal cannula oxygen throughout the study period. Measured oxygen content was obtained from the directly measured data from this formula: oxygen content (vol%) = oxygen saturation/100 × hemoglobin content (g/dL) × 1.34 × PO₂ (mm Hg). Myocardial oxygen uptake (mL O₂/L) was found from this equation: myocardial oxygen uptake = arterial oxygen content (mL O₂/L) – coronary sinus oxygen content (mL O₂/L). Left ventricular power (W) was found as follows: left ventricular power = [(CO)(10−6 m³/L)(peak LV pressure)](133.3 Pa/mm Hg)(60 s/min). Myocardial oxygen consumption (MVO₂) is proportional to (CBF)(AVDVO₂). Left ventricular mechanical efficiency is the ratio of left ventricular power to energy expenditure calculated as left ventricular power divided by MVO₂. Global myocardial oxygen consumption can only be approximated because global CBF cannot be estimated by the Doppler and QCA assessment of a single coronary artery. Thus, the calculated MVO₂ in this study...
TABLE 1. Right-Heart and Systemic Hemodynamics at Baseline and 30 Minutes After Initiation of Levosimendan

| Hemodynamic Variable       | Baseline       | At 30 min     | P  
|---------------------------|----------------|---------------|------
| Heart rate, bpm           | 77±13          | 91±19         | 0.002 |
| Right-heart hemodynamics  |                |               |      |
| Right atrium, mm Hg       | 5.0±3.3        | 3.3±3.7       | 0.05 |
| Pulmonary artery systolic, mm Hg | 30.3±11.0 | 27.0±15.9     | 0.15 |
| Pulmonary artery mean, mm Hg | 19.7±9.5     | 17.4±12.6     | 0.26 |
| Pulmonary capillary wedge, mm Hg | 11.2±8.9     | 7.1±8.0       | 0.009 |
| Cardiac output, L/min     | 4.5±1.4        | 4.9±1.4       | 0.04 |
| Systemic hemodynamics     |                |               |      |
| Aortic mean, mm Hg        | 94±21          | 82±16         | 0.03 |
| Systemic vascular resistance, dyne·s·cm⁻¹ | 1659±431 | 1360±346     | <0.001 |
| Stroke volume index, mL/m² | 29.2±7.9      | 27.2±7.8      | 0.26 |
| Stroke work index, g/m²    | 49.1±23.2      | 41.1±14.3     | 0.16 |
| Left ventricular power, W | 1.33±0.59      | 1.30±0.54     | 0.81 |

is an approximation of global MVO₂. Similarly, the calculated left ventricular myocardial efficiency is an approximation.

Statistical Analysis

Data are presented as mean values and SDs for continuous variables. Differences between baseline and levosimendan treatment values were assessed by use of a 2-tailed paired t test or repeated-measures ANOVA when appropriate. Changes in coronary flow velocity were assessed with a multiple regression analysis that allowed for the repeated measures at baseline and 5, 15, and 30 minutes for each subject. Specifically, we used the method of generalized estimating equations with an unstructured working correlation matrix. This method does not make model assumptions about the form of the correlation between the repeated measurements. Two-tailed values of P<0.05 were considered significant.

Results

Patient Population

Ten adult patients were enrolled. Eight were men, and the mean age was 60±14 years (range, 42 to 86 years). Six patients had coronary artery disease with ≥1 coronary artery with ≥75% diameter stenosis, and 3 patients had a history of prior myocardial infarction. Two patients had diabetes mellitus, 7 had a history of hypertension, 7 had hyperlipidemia, and 4 had a clinical diagnosis heart failure (3 ischemic, 1 nonischemic cardiomyopathy). Clinical indication for cardiac catheterization included angina (n=6), heart failure (n=2), atypical chest pain (n=1), and annual surveillance after orthotopic heart transplantation.

Cardiac medication use included the following: ACE inhibitors or angiotensin receptor blockers (80%), β-blockers (50%), calcium channel blockers (30%), nitrates (20%), digoxin (10%), and statins (70%).

Right-Heart Hemodynamics

Heart rate increased by 8% at 15 minutes after levosimendan was begun (P=0.01) and by 18% at 30 minutes compared with baseline (P=0.002 versus baseline; Table 1). Mean right atrial pressure decreased by 34%, and mean pulmonary capillary wedge pressure decreased by 37% during the levosimendan infusion. Cardiac output by the thermodilution method increased by 9% from baseline to 30 minutes (P=0.04). Pulmonary artery pressure and pulmonary vascular resistance were unchanged.

Systemic Hemodynamics

Levosimendan was well tolerated in all patients, and symptomatic hypotension was not observed. Mean arterial pressure decreased by 13%, and systemic vascular resistance decreased by 18% from baseline to 30 minutes (Table 1). There were trends toward decreased stroke volume index and stroke work index. Left ventricular power was unchanged.

Echocardiography

Echocardiographic measures of left ventricular function at baseline and 30 minutes after levosimendan was started are shown in Table 2. At baseline, 4 patients had a left ventricular ejection fraction <40%, and the mean left ventricular ejection fraction for the entire cohort was 46±18% (range, 21% to 71%). Although there was no change in left ventricular end-diastolic volume index, there was a significant 13% decrease in left ventricular end-systolic volume index (P=0.01) and a 20% increase in ejection fraction (P=0.009). Meridional systolic wall stress decreased 48% (P=0.009). There was no significant change in E/e′.

Coronary Hemodynamics

The left anterior descending artery was used for coronary hemodynamic measurements in 7 patients; left circumflex, in 2 patients; and right coronary artery, in 1 patient. The left anterior descending coronary artery was not used in all patients because of the following angiographic findings: 2 patients had severe disease in the left anterior descending, and 1 patient had severe left main coronary artery disease. Eight of the 10 patients had adequate Doppler flow velocity measurements throughout the 30-minute study period. The intracoronary APV was unchanged at baseline (23.9±9.0 cm/s) through 10 minutes. The APV had a 10% increase to 26.0±9.8 cm/s at 15 minutes (P=0.28) and 26.4±9.2 cm/s at 30 minutes (P=0.04; Figure 1). Mean coronary artery diameter increased by 10% from 2.9±0.9 mm at baseline to 3.2±0.9 mm at 15 minutes (P=0.001) and 3.3±1.0 mm at 30 minutes (14% increase and P=0.01 versus baseline; Figure 2). Coronary blood flow increased by 41% from 44±14 mL/min at baseline to 62±31 mL/min at 15 minutes (P=0.04) and 64±25 mL/min at 30 minutes (P=0.02; Figure 3). Coronary resistance decreased by 24% from 2.1±1.0 mm Hg·min/mL at baseline to 1.6±0.8 mm Hg·min/mL at 15 minutes (P=0.0006) and 1.4±0.7 mm Hg·min/mL at 30 minutes (P=0.03; Figure 4).

TABLE 2. Echocardiographic Hemodynamics at Baseline and 30 Minutes After Initiation of Levosimendan

| Echocardiographic Variable | Baseline       | At 30 min     | P  
|----------------------------|----------------|---------------|------
| LVEDVI, mL/m²              | 66±36          | 65±36         | 0.80 |
| LVESVI, mL/m²              | 41±32          | 35±32         | 0.01 |
| Ejection fraction, %       | 46±18          | 55±22         | 0.009 |
| Meridional wall stress, dyne/cm² | 140±83       | 73±48         | 0.009 |
| E/e′                       | 6.1±3.2        | 4.9±1.6       | 0.26 |

LVEDVI indicates left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index.
Coronary sinus sampling was performed in 9 patients. Coronary sinus oxygen content increased by 10% from 6.8 ± 1.3 vol% at baseline to 7.5 ± 1.8 vol% at 30 minutes (P = 0.14). Arterial oxygen content decreased slightly from 17.9 ± 2.1 vol% at baseline and 17.6 ± 2.1 vol% at 30 minutes (n = 10; P = 0.02). Myocardial oxygen uptake decreased by 9% from 11.2 ± 1.7 vol% at baseline to 10.2 ± 1.5 vol% at 30 minutes (P = 0.04; Figure 5). Both patients with and without coronary artery disease and those with and without heart failure had a reduction in myocardial oxygen uptake during the levosimendan infusion. Myocardial oxygen consumption had a nonstatistically significant increase by 35% (n = 7; P = 0.15). Left ventricular mechanical efficiency was unchanged after levosimendan administration (27.6 ± 17.3% at baseline versus 20.0 ± 8.5% at 30 minutes; n = 7; P = 0.30).

Discussion
We demonstrated that intravenous administration of levosimendan exerts vasodilatory effects on both the coronary conductance and resistance arteries. The dose of levosimendan used in this study was the clinically used bolus dose for patients with decompensated heart failure. The magnitudes of coronary epicardial vasodilation and augmentation in coronary blood flow in response to levosimendan were consistent with prior studies of intracoronary infusion in porcine arteries.

The intravenous positive inotropic agents used commonly for management of patients with decompensated heart failure are β-adrenergic agonists and phosphodiesterase III/IV inhibitors. These agents increase myocardial contractility by increasing the intracellular calcium concentration via an increase in cAMP and activation of the protein kinase pathway. However, an increased intracellular calcium concentration may lead to calcium overload and subsequent adverse effects on cardiac rhythm and energy consumption. Although β-adrenergic agonists and phosphodiesterase inhibitors produce rapid hemodynamic improvement, these agents may increase myocardial ischemia or arrhythmias. These agents have been associated with an adverse effect on short-term survival.

A novel calcium-sensitizing agent with both inotropic and vasodilatory properties, levosimendan is being investigated for treatment of patients with decompensated heart failure. Levosimendan is a pyridazinone-dinitrile derivative that increases myofilament calcium sensitivity by binding to cardiac troponin C in a calcium-dependent fashion. Levosimendan binds selectively to calcium-saturated cardiac troponin C, stabilizing that conformation of troponin C that triggers myocyte contraction. Because levosimendan dissociates from cardiac troponin C at a low calcium concentration, this agent does not impair diastolic function. Because calcium sensitization enhances cardiac contractility without increasing intracellular calcium concentration, the risk of developing ischemia or arrhythmias should be lowered.
Figure 5. Myocardial oxygen uptake at baseline and 30 minutes (p=0.04; n=9).

The vasodilatory properties of levosimendan are believed to act via opening of ATP-sensitive potassium channels in vascular smooth muscle. Vasodilation has been demonstrated in vascular smooth muscle cells from isolated porcine coronary arteries, coronary vascular smooth muscle in isolated guinea pig hearts, and rat mesenteric smooth muscle. The systemic vascular vasodilatory effects lead to a reduction in both preload and afterload.

In this study, we observed vasodilatory responses to levosimendan in both conductance and resistance coronary arteries. The conductance epicardial coronary arteries dilated with a 10% to 14% increase in coronary diameter at 15 and 30 minutes (Figure 2). There was a 10% increase in average peak velocity beginning at 15 minutes after the initiation of levosimendan that continued through 30 minutes, indicating resistance vessel dilatation (Figure 1). Because the coronary perfusion pressure decreased after the levosimendan infusion, the absence of a decline in coronary velocity indicates primary vasodilation with a decrease in coronary resistance. Despite the increase in contractility by echocardiographic measures, the increase in coronary sinus oxygen content also suggests primary coronary vasodilatation.

We also demonstrated that myocardial oxygen uptake decreased 30 minutes after the initiation of levosimendan. Systemic arterial pressure, pulmonary capillary wedge pressure, and systemic vascular resistance significantly decreased with levosimendan administration; heart rate and cardiac output increased. These hemodynamic changes are in contrast to what is observed with other available inotropic medications used in heart failure. The positive inotropic agent dobutamine is commonly used to manage decompensated heart failure. In contrast to levosimendan, dobutamine increases both coronary blood flow and myocardial oxygen consumption.

Nesiritide, a recombinant B-type natriuretic peptide used in patients with decompensated heart failure, increases coronary blood flow, decreases myocardial oxygen consumption but has no significant inotropic effects on contractility.

Our findings on the effect of levosimendan of decreasing myocardial oxygen extraction are supported by prior studies with levosimendan. In a study assessing myocardial oxygen consumption using dynamic PET with 11C-acetate in healthy volunteers, dobutamine significantly increased oxygen consumption by 58%, whereas levosimendan and nitroprusside had neutral effects. Although levosimendan had no effect on energy-consuming substances, dobutamine increased free fatty acid levels by >200%. In another study evaluating coronary artery hemodynamics in 23 anesthetized patients immediately after CABG surgery with a thermodilution coronary sinus catheter, levosimendan improved systolic function without increasing myocardial oxygen consumption. At 30 minutes, the 24-μg/kg levosimendan dose increased coronary artery blood flow by ~30 mL/min. This finding is very consistent with our finding of a 20-mL/min increased flow in a single coronary artery that measured coronary artery blood flow with intracoronary Doppler velocity and QCA.

Ukkonen et al assessed myocardial oxygen consumption in 8 hospitalized heart failure patients using dynamic PET imaging. Myocardial blood flow increased significantly by 34% with levosimendan compared with placebo. These investigators reported that despite increases in cardiac output, myocardial oxygen consumption was unaltered by levosimendan. Similar to our findings, there was no significant change in left ventricular efficiency with levosimendan.

Our study also suggests that levosimendan has the potential to decrease myocardial oxygen demand. There were a significant decrease in systolic wall stress and no significant increase in the heart rate–blood pressure product. The combined effects of primary coronary vasodilation, reduced myocardial oxygen extraction, reduced preload and afterload, and reduced myocardial oxygen extraction indicate that levosimendan has a favorable hemodynamic profile for management of patients with decompensated heart failure.

Study Limitations
This study was performed in patients without decompensated heart failure. It is possible that the decrease in myocardial oxygen extraction may be greater in decompensated patients. Although 6 of the 10 patients had hemodynamically significant coronary artery disease, coronary arteries with significant epicardial disease were excluded from the hemodynamic assessment of coronary blood flow. Therefore, the hemodynamic coronary effects of levosimendan in those arteries with significant coronary artery disease require further study. This study did not directly address the clinical implications of levosimendan-induced favorable changes in coronary hemodynamics. We continuously monitored changes in coronary artery velocity with the Doppler-tipped guidewire, whereas we measured changes in coronary artery diameter only at 15- and 30-minute intervals. It is possible that there were more rapid changes in coronary diameter that we were unable to detect with coronary angiography performed at predetermined time points. The limitations of QCA analyses and the Doppler-tipped guidewire measurements have been described previously.

Conclusions
Levosimendan acts as a direct coronary vasodilator that decreases impedance in the coronary conductance and resistance arteries and the peripheral arterial circulation. Left ventricular filling pressure decreased, coronary artery blood flow increased, coronary artery resistance decreased, and myocardial oxygen uptake decreased during levosimendan infusion. Echocardiographic measures showed increased systolic function and de-
creased wall stress. The combination of improved systolic function, increased cardiac output, increased coronary artery blood flow, and reduced myocardial oxygen extraction showed that levosimendan has the potential to produce favorable effects on systemic and coronary hemodynamics and to improve myocardial metabolic function.

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