Alteration of Contractile Function and Excitation–Contraction Coupling in Dilated Cardiomyopathy

Gerd Hasenfuss, Louis A. Mulieri, Bruce J. Leavitt, Paul D. Allen, Joe R. Haeberle, and Norman R. Alpert

Myocardial failure in dilated cardiomyopathy may result from subcellular alterations in contractile protein function, excitation–contraction coupling processes, or recovery metabolism. We used isometric force and heat measurements to quantitatively investigate these subcellular systems in intact left ventricular muscle strips from nonfailing human hearts (n=14) and from hearts with end-stage failing dilated cardiomyopathy (n=13). In the failing myocardium, peak isometric twitch tension, maximum rate of tension rise, and maximum rate of relaxation were reduced by 46% (p=0.013), 51% (p=0.003), and 46% (p=0.018), respectively (37°C, 60 beats per minute). Tension-dependent heat, reflecting the number of crossbridge interactions during the isometric twitch, was reduced by 61% in the failing myocardium (p=0.006). In terms of the individual crossbridge cycle, the average crossbridge force–time integral was increased by 33% (p=0.04) in the failing myocardium. In the nonfailing myocardium, the crossbridge force–time integral was positively correlated with the patient’s age (r=0.86, p<0.02), whereas there was no significant correlation with age in the failing group. The amount and rate of excitation–contraction coupling–related heat evolution (tension-independent heat) were reduced by 69% (p=0.024) and 71% (p=0.028), respectively, in the failing myocardium, reflecting a considerable decrease in the amount of calcium released and in the rate of calcium removal. The efficiency of the metabolic recovery process, as assessed by the ratio of initial heat to total activity-related heat, was similar in failing and nonfailing myocardium (0.54±0.03 versus 0.50±0.02, p=0.23). Thus, in failing dilated cardiomyopathy, contractile protein function is altered with an increased force–time integral of the individual crossbridge cycle. However, this alteration does not explain failure since the same changes are present in nonfailing myocardium from older patients. The findings suggest that reduced tension generation in failing dilated cardiomyopathy primarily results from disturbed excitation–contraction coupling processes with a reduced amount of calcium released and a reduced rate of calcium removal. (Circulation Research 1992;70:1225–1232)

KEY WORDS • dilated cardiomyopathy myocardial failure • crossbridges • calcium cycling • human myocardium

Heart failure in dilated cardiomyopathy is characterized clinically by decreased ejection fraction, reduced rates of left ventricular pressure rise and fall, and elevated left ventricular end-diastolic pressure and end-diastolic volume. The subcellular defects underlying reduced systolic and diastolic function in this disease are not well understood. Basically, three subcellular systems may be involved in the development of myocardial failure: 1) contractile proteins,1–3 2) excitation–contraction coupling processes,4–6 and 3) recovery metabolism.7–9

Previous work on isolated human myocardium performed at low temperature (30°C) and rates of stimulation (0.6–60 beats per minute) indicates that contractile failure in myopathic human myocardium depends on stimulation frequencies.10–12 In other words, whether or not an abnormality in the diseased myocardium is obvious may critically depend on experimental conditions.

The recent development of a method for dissecting thin viable muscle strips from larger pieces of human myocardium13 makes it possible to investigate these subcellular systems in the intact muscle by means of a myothermal method14 under physiological conditions (37°C, 60 beats per minute). Heat evolution represents the entire metabolic energy turnover during the isometric twitch. Total activity-related heat can be partitioned into the heat evolution of the contractile proteins, the excitation–contraction coupling system, and the recovery system. These measurements in conjunction with the mechanical performance provide quantitative information on the extent and rate of the reactions involved.
in crossbridge interaction, excitation–contraction coupling, and recovery metabolism.\textsuperscript{15–17}

In the present study, we used sensitive antimony-bismuth thermopiles\textsuperscript{14} and isometric force gauges to measure isometric heat and force output of muscle strips from isolated failing and nonfailing human myocardium to investigate 1) the number of crossbridge interactions and the function of contractile proteins, 2) the amount of calcium cycling and the rate of calcium removal, and 3) the efficiency of metabolic recovery processes.

**Materials and Methods**

**Patients and Muscle Preparation**

**Failing myocardium.** Thirteen left ventricular muscle strips and trabeculae carneaee were dissected from hearts obtained from six patients with end-stage dilated cardiomyopathy (New York Heart Association class IV) undergoing cardiac transplantation surgery. Five had idiopathic dilated cardiomyopathy, and in one patient cardiomyopathy had developed after adriamycin treatment for lung cancer. The mean age of the patients was 48±6 years. One was female, and five were male. Average ejection fraction measured by angiocardiology or echocardiography was 13±1%. Previous medication included digoxin (n=6), furosemide (n=5), metolazone (n=1), milrinone (n=1), dobutamine (n=2), dopamine (n=1), enalapril (n=1), captopril (n=3), diltiazem (n=2), procainamide (n=1), quinidine (n=1), warfarin (n=3), and aspirin (n=1). Excised hearts were washed of blood with chilled saline solution. Left ventricular myocardium was dissected from the endocardial and epicardial surface of the ventricle within 20 minutes of cardiectomy.

**Nonfailing myocardium.** Nonfailing myocardium (14 muscle strip preparations) was prepared from left ventricular biopsies obtained during coronary artery bypass surgery from seven patients with coronary artery disease and normal left ventricular function. The myocardial biopsies (1.5×1.5×12 mm) were dissected from the epicardial surface with a scalpel immediately after complete cardioplegia. The mean age of the patients was 60±4 years. The average angiocardioicographical ejection fraction was 67±2%. Two patients were female, and five were male. Previous medication included diltiazem (n=4), verapamil (n=1), isosorbide dinitrate (n=4), nifedipine (n=1), dipyridamole (n=1), atenolol (n=1), propranolol (n=1), phenytoin (n=1), lovastatin (n=1), and aspirin (n=4).

The study protocol was reviewed and approved by the Committee on Human Research of the University of Vermont. Patients gave written informed consent before participating in the study. No side effects due to the biopsy procedure occurred.

**Muscle Strip Preparation**

The excised myocardium was immediately submerged in a protective solution at room temperature and oxygenated by bubbling with 95% O\textsubscript{2}–5% CO\textsubscript{2}. The protective solution consists of Krebs-Ringer solution to which 2,3-butanedione monoxime was added.\textsuperscript{13} The solution contained (mM) Na\textsuperscript{+} 152, K\textsuperscript{+} 3.6, Cl\textsuperscript{−} 135, HCO\textsubscript{3}– 25, Mg\textsuperscript{2+} 0.6, H\textsubscript{2}PO\textsubscript{4}– 1.3, SO\textsubscript{4}2– 0.6, Ca\textsuperscript{2+} 2.5, glucose 11.2, and 2,3-butanedione monoxime 30, along with 10 IU/l insulin. To prepare the experimental intact muscle strip, the excised myocardium was clamped between the ends of plastic rods and submerged in protective solution in a dissection chamber.\textsuperscript{13} The myocardium could be rotated axially to facilitate dissection, which was performed with microdissection scissors (6-mm blade) and forceps under a ×10 binocular microscope. Strips of muscle tissue were dissected from the main piece and transferred to a similar but smaller dissection chamber also filled with protective solution where sculpting to final dimensions (cross-sectional area, <0.5 mm\textsuperscript{2} in nonfailing myocardium and <0.7 mm\textsuperscript{2} in failing myocardium) and attachment of ligatures were carried out. These cross-sectional areas have been shown to be below the critical cross-sectional area for adequate oxygenation (37°C, 60 beats per minute) on the basis of the Paradise protocol performed in studies from tissue of the same hearts in our laboratory.\textsuperscript{18,19} Strips were cut parallel to muscle cell orientation. Loops of 4-0 noncapillary braided silk, previously wired with a 25-μm-diameter platinum stimulating electrode wire, were attached to the ends of the preparation with silk ligatures.\textsuperscript{14} On completion of the preparation, the muscle strip was allowed to recover in oxygenated, room-temperature, protective solution for 15–30 minutes. To perform the heat and mechanical measurements, the muscle was mounted in contact with the active region of a thermopile and connected to the force gauge. The muscle and thermopile were then submerged in normal oxygenated Krebs-Ringer solution to wash out the 2,3-butanedione monoxime. After an equilibration period of 60–90 minutes, the muscle was stretched gradually (in 0.05–0.1-mm steps) to the length at which maximum steady-state twitch force was reached (\(I_{\text{max}}\)). When steady-state conditions were reached at \(I_{\text{max}}\), the chamber was drained, and thermal and tension signals were recorded during repetitive stimulation as described previously\textsuperscript{15–17} (Figure 1). All measurements were performed at \(I_{\text{max}}\) with a stimulation rate of 60 beats per minute and a temperature of 37°C. Throughout this article, active tension values above resting tension are given. At the end of each experiment, muscle length at \(I_{\text{max}}\) was measured, and blotted weight of this segment was obtained. Cross-sectional area for normalization of force values was calculated as the ratio of blotted weight to muscle length (\(l_{\text{max}}\)).

**Heat Terms, Myothermal Measurements, and Thermal Analysis**

**Definition of heat terms.** Under steady-state isometric conditions, all of the energy turned over by the muscle is liberated as heat by the end of the twitch. The total activity-related heat is divisible into initial and recovery components. Initial heat is composed of the tension-dependent heat and tension-independent heat. Tension-dependent heat results from high-energy phosphate hydrolysis by cycling crossbridges. Assuming that one high-energy bond is hydrolyzed during each crossbridge cycle,\textsuperscript{20} tension-dependent heat directly reflects the number of crossbridge interactions during the isometric twitch.

Tension-independent heat reflects high-energy phosphate hydrolysis by sarcoplasmic reticulum and sar-
colemmal calcium pumps predominantly and, to a lesser extent, high-energy phosphate hydrolysis by sarcolemmal Na,K-ATPases and other ATP-using pumps. The initial heat is calculated from the temperature difference \( t_1 \) (solid vertical arrow). The area between the temperature signal and the horizontal resting baseline (crosshatched area \([t_1-d]\)) is used to calculate the total activity-related heat. The resting baseline temperature is obtained by allowing the muscle to cool to a constant temperature.

**Figure 1.** Recordings of the muscle temperature (upper tracing) and force signal (lower tracing) from an isometrically contracting human left ventricular myocardial strip. The initial heat is calculated from the temperature difference \( t_1 \) (solid vertical arrow). The area between the temperature signal and the horizontal resting baseline (crosshatched area \([t_1-d]\)) is used to calculate the total activity-related heat. The resting baseline temperature is obtained by allowing the muscle to cool to a constant temperature.

For measurements of myosin content, segments of left ventricular myocardium from seven nonfailing hearts and seven hearts with dilated cardiomyopathy were frozen in liquid nitrogen. The frozen tissue was then pulverized, suspended in dry ice–cooled aceton plus 10% trichloroacetic acid (wt/vol) and 10 mM dithiothreitol, and slowly thawed at 5°C. The sample was sedimented at 13,000g for 1 minute, and the pellet was resuspended in aceton plus 10 mM dithiothreitol. After two additional washes with aceton plus 10 mM dithiothreitol, the pellet was dried in a Speed Vac lyophilizer (Savant Instruments Inc., Framingham, N.Y.). The dried pellet was weighed, and 5 mg was dissolved in 1 ml of boiling sodium dodecyl sulfate buffer (62.5 mM Tris base, 3% sodium dodecyl sulfate, and 20% glycerol). This extract was sedimented at 13,000g for 5 minutes, and the supernatant was processed by sodium dodecyl sulfate–polyacrylamide gel electrophoresis on 6% gels using the buffer system of Porzio and Pearson. Rabbit skeletal muscle myosin was run on the same gels as a standard. The protein
content of the standards was determined using an extinction coefficient of 5.3 (E$_{280}$ in Reference 23). Gels were stained with Coomassie blue, and protein was determined by densitometric scanning.

**Statistical Analysis**

Data are expressed as mean±SEM. Differences between failing and nonfailing myocardium were determined by the nonpaired t test. A value of $p<0.05$ was accepted as statistically significant.

**Results**

In failing compared with nonfailing human myocardium, peak twitch tension was reduced by 46%, and maximum rate of tension rise and fall were reduced by 51% and 46%, respectively (Table 1). Time to peak tension was prolonged in the failing myocardium, whereas there was no difference in the time to 50% relaxation (Table 1).

A comparison of the isometric force and initial heat output for nonfailing and failing human myocardium is presented in Figure 2. Initial heat, reflecting high-energy phosphate hydrolysis during the isometric twitch was significantly reduced by 61% in failing compared with nonfailing human myocardium (Table 2). To understand the subcellular alterations underlying this reduced heat evolution, initial heat was partitioned into its two components, tension-dependent heat and tension-independent heat. Tension-dependent heat, reflecting high-energy phosphate hydrolysis by crossbridges, was reduced by 61% in failing compared with nonfailing myocardium (Figure 3, Table 2). In terms of the individual crossbridge cycle, the average crossbridge force–time integral was increased by 33% in failing compared with nonfailing myocardium (Figure 3). There was a close linear correlation between the crossbridge force–time integral and the age of the patients with normal left ventricular function (Figure 4). The crossbridge force–time integral was not significantly correlated with the age of the patients in the failing myocardium ($r=-0.45$, $p>0.05$) (Figure 4).

Tension-independent heat, reflecting the high-energy phosphate hydrolysis of excitation–contraction coupling processes and, thus, of calcium pumps, predominantly, was reduced by 69% in the failing myocardium (Figure 5, Table 2). This indicates a considerable reduction in the amount of calcium cycling during each isometric twitch. Average tension-independent heat rate, reflecting the rate of calcium removal, was similarly reduced (Figure 5) in the failing myocardium.

In addition to initial heat, total activity-related heat includes recovery heat, which is liberated by metabolic recovery processes. The ratio of initial heat to total activity-related heat, reflecting the efficiency of metabolic recovery processes, was similar in nonfailing and failing myocardium (Table 2).

Myosin content was 0.176±0.009 μg/μg dry tissue wt in nonfailing myocardium and 0.141±0.011 μg/μg dry tissue wt in failing myocardium ($p=0.03$).

**Discussion**

In the present study, isometric heat and force measurements were used to compare the function of subcellular systems in failing and nonfailing human myocardium. The alterations of the mechanical parameters measured in isolated muscle strips from failing human myocardium are consistent with the clinical observation of reduced systolic and diastolic left ventricular performance in patients with dilated cardiomyopathy. In the failing myocardium, under physiological conditions of temperature and stimulation frequency, peak twitch...
tension was reduced by 46%, maximum rate of tension rise was reduced by 51%, and maximum rate of tension fall was reduced by 46%. These findings are different from those of other investigators who suggested no significant difference in contractile force of the myocardium from failing and nonfailing human hearts.6,24,25 The apparent discrepancy between these studies and the present findings can be explained by differences in experimental conditions, e.g., the lower stimulation frequencies used in other studies. As was shown recently, an increase in stimulation frequency has positive inotropic effects up to an average of 166 beats per minute in nonfailing human myocardium.26 However, the force–frequency relation was inverted in myocardium from dilated cardiomyopathic hearts in which force was maximal at an average of 36 beats per minute and decreased with higher pacing rates.19,26 Accordingly, Feldman et al10 demonstrated that peak twitch tension increased from 20 beats per minute to 60 beats per minute in nonfailing but not in failing human myocardium (Figure 1 of Reference 10). Similar findings were obtained by Phillips et al11 and Gwathmey et al.12 Thus, whether or not there is a contractile deficit in failing compared with nonfailing human myocardium depends on stimulation frequency. Differences in contractile force between failing and nonfailing human myocardium are present at physiological frequencies (60 beats per minute and higher) but absent at lower frequencies. It is interesting to note that our tension values are 1.7 to 7.5 times higher in failing myocardium (13.9±2.0 mN/mm²) and 3.6 to 5.8 times higher in nonfailing myocardium (25.9±3.9 mN/mm²) than those measured in previous studies by others.5,10,11,24,27,28 Higher tension values in the present study most likely are due to a new dissection procedure that has been shown to minimize damage during dissection of the myocardium.13

Heat measurements were performed in order to investigate the subcellular correlates of the contractile deficit in the failing human myocardium present at a stimulation frequency of 60 beats per minute. From these measurements, the reduced contractile force in failing myocardium can be attributed to a decreased number of crossbridge interactions during each contraction–relaxation cycle. This is indicated by the 61% reduction in tension-dependent heat from high-energy phosphate hydrolysis by crossbridges. A decrease in the number of crossbridge interactions and in force production could result from reduced contractile protein content per cross section or from reduced activation of contractile proteins.

Measurements of myosin content performed in the present study indicate that contractile protein content may be reduced by 20% in the failing myocardium. This is in accord with morphometric measurements of Hirzel et al.,29 who reported that nonmuscle tissue content is increased from 4% to 23% in myocardium from dilated cardiomyopathic hearts.29 After a correction for 20% reduction in contractile protein content in the failing myocardium, peak twitch tension and tension-dependent heat would still be reduced by 33% and 51%, respectively. As indicated from tension-independent heat measurements, the decreased force production and

**TABLE 2.** Myothermal Data in the Human Myocardium at 37°C and 1 Hz

<table>
<thead>
<tr>
<th></th>
<th>Initial heat (mJ/g)</th>
<th>Tension-dependent heat (mJ/g)</th>
<th>Tension-independent heat (mJ/g)</th>
<th>Initial heat/total heat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfailing myocardium</td>
<td>3.89±0.66</td>
<td>3.39±0.59</td>
<td>0.51±0.13</td>
<td>0.50±0.02</td>
</tr>
<tr>
<td>Failing myocardium</td>
<td>1.50±0.26</td>
<td>1.34±0.22</td>
<td>0.16±0.05</td>
<td>0.54±0.03</td>
</tr>
<tr>
<td>p</td>
<td>0.004</td>
<td>0.006</td>
<td>0.024</td>
<td>0.23</td>
</tr>
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Values are mean±SEM. Total heart, total activity-related heart.

**FIGURE 3.** Bar graphs showing crossbridge cycling–related heat evolution (left panel) and average crossbridge force–time integral (right panel) in failing (F) and nonfailing (NF) human myocardium. Tension-dependent heat results from high-energy phosphate hydrolysis by crossbridges and thus reflects the number of crossbridge interactions during the isometric twitch. Average crossbridge force–time integral is calculated from the ratio of twitch force–time integral and tension-dependent heat.17

**FIGURE 4.** Scatterplot showing the relation between the average force–time integral of the individual crossbridge cycle (average value for each heart) and age of patients in nonfailing (○) and failing (□) human myocardium. There is a significant correlation between these parameters in the nonfailing hearts.
number of crossbridge interactions in the failing myocardium predominantly result from reduced activation of contractile proteins. Tension-independent heat was 69% lower in the failing myocardium (or 61% lower if 20% reduction in number of myocytes is considered), indicating a considerable reduction in the number of calcium ions released during the isometric twitch. Consequently, fewer crossbridges may be recruited in the failing myocardium. Reduced calcium release in the failing myocardium goes along with a reduced rate of calcium removal (lower average tension-independent heat rate) also observed in the failing myocardium. The latter is consistent with recent aequorin measurements that showed a prolongation of the aequorin signal in the failing human myocardium. This study also suggested that disturbed calcium removal may be the primary cause of impaired relaxation in the failing human heart. A reduced rate of calcium removal could result from a decreased number of sarcoplasmic reticulum calcium pumps, due to a lower density of pumps or a reduced amount of sarcoplasmic reticulum per cell. Calcium uptake by isolated sarcoplasmic reticulum of failing human hearts was shown to be reduced in one study but was not different from the control value in another. A decreased number of sarcoplasmic reticulum calcium pumps in the failing human heart was suggested from Ca\(^{2+}\)-ATPase mRNA measurements. On the basis of these findings, the mechanism for the reduction in calcium release may be impaired sarcoplasmic reticulum calcium reuptake with the consequent depletion of the sarcoplasmic reticulum calcium content. Low cytosolic cAMP concentrations may be additionally involved in disturbed sarcoplasmic reticulum calcium handling. Although the aequorin studies have been interpreted to indicate that there is no reduction in the amount of activation in dilated cardiomyopathy, we believe that these studies have not ruled out decreased activation as a mechanism for the reduced twitch tension we observed in failing myocardium. The present study was done on left ventricular muscle strips at 37°C with stimulation frequencies of 60 beats per minute, whereas most aequorin studies were performed on right ventricular trabeculae at 30°C with stimulation frequencies of 20 beats per minute. Under those conditions, twitch tension of failing human myocardium was not significantly different from normal.

In addition to a reduced number of crossbridge interactions, the force-generating process within the individual crossbridge cycle is significantly altered in the failing human heart. The average force–time integral of the individual crossbridge cycle is increased by 33% in failing myocardium. This may result from increased crossbridge force, increased attachment time, or both. Increased crossbridge attachment time would be consistent with reduced myofibrillar Mg-ATPase activity observed in failing myocardium from dilated cardiomyopathic hearts. An increased crossbridge force–time integral and reduced myofibrillar ATPase activity have been attributed to alterations in myosin heavy chain isoforms in animal models of myocardial hypertrophy. Since similar isoform shifts are not observed in the human heart, alterations in the crossbridge cycle may be due to changes in the light chains of the myosin or thin-filament regulation of the crossbridge cycle.

Interestingly, in the nonfailing myocardium, the crossbridge force–time integral was positively correlated with the patient’s age, whereas there was no significant correlation with age in the failing group. This may indicate that aging of the contractile proteins occurs in the nonfailing human myocardium as it has been observed in animal experiments. The average crossbridge force–time integral in failing myocardium was comparable to the values obtained in nonfailing myocardium from older patients.

An increased crossbridge force–time integral may have two different consequences with respect to myocardial function. On the one hand, an increased crossbridge force–time integral may be favorable from an energy economy point of view, since a greater force or force–time integral is produced per unit of high-energy phosphate hydrolyzed. On the other hand, prolonged crossbridge attachment time may result in reduced rates of relaxation and reduced shortening velocity and may prevent the myocardium from developing high power output. Therefore, an increased crossbridge force–time integral in the senescent myocardium may be related to the clinical findings of altered diastolic filling and diminished exercise capacity in older patients. In the failing human heart, an increased crossbridge force–time integral may further aggravate the effects of disturbed excitation–contraction coupling on myocardial function, with respect to relaxation and power development.

Previous biochemical studies have suggested impaired mitochondrial function in the failing human heart. Since efficiency of the metabolic recovery processes is unaltered in the failing myocardium despite a marked decrease in contractile performance, disturbed mitochondrial oxidative phosphorylation is an unlikely candidate for the cause of heart failure in these dilated cardiomyopathic hearts. However, one cannot exclude the possibility, based on the present data, that mitochondrial dysfunction may occur during periods of higher metabolic demand (i.e., increased heart rate), as was recently shown in Syrian hamster cardiomyopathy. Under those circumstances, a reduced energy supply could further impair myocardial function.
In summary, disturbed excitation–contraction coupling with reductions in the amount of calcium release and the rate of calcium removal provides a potential subcellular explanation for the decreased myocardial function in failing hearts with dilated cardiomyopathy. The effect of disturbed excitation–contraction coupling on myocardial function may be aggravated by alterations in the kinetics of the individual crossbridge cycle involving an increased crossbridge force–time integral. Since contractile deficit in failing human myocardium depends on stimulation frequency, the subcellular alterations observed at 60 beats per minute may be absent at lower frequencies and more pronounced at higher stimulation rates. Further studies are warranted to investigate the frequency dependence of contractile protein function and excitation–contraction coupling processes in the failing human heart.

It should be pointed out that, because of the surgical procedures, nonfailing myocardium was dissected from the epicardial surface of the heart during high potassium cardioplegia and immersed immediately in protective solution, whereas failing myocardium was dissected from the endocardial and the epicardial surface (without cardioplegia) and submerged in protective solution 10–20 minutes after cardiectomy. Therefore, these differences in preparation techniques may have affected the viability of the failing myocardium. However, we do not believe that these differences caused reduced tension development in the failing myocardium for the following reasons: 1) In two muscle strips removed from a nonfailing explanted heart without cardioplegia, peak twitch tension was comparable to values obtained in strips that were dissected from hearts during high potassium cardioplegia. 2) There was no relation between time of submersion in protective solution (between 10 and 20 minutes after cardiectomy) and peak twitch tension values of muscle strips from failing hearts. 3) As presented in “Materials and Methods,” peak twitch tension was similar in muscle strips from the epicardial and the endocardial surface of the failing hearts. 4) The finding of similar tension values in nonfailing and failing myocardium at 30 beats per minute may indicate that differences in tension at higher frequencies result from functional alterations rather than from different numbers of viable myocytes. In addition, it seems unlikely that previous medication, including positive inotropic drugs (digoxin) in heart-failure patients and negative inotropic drugs (β-receptor blockers, calcium antagonists) in patients with normal left ventricular function, might have been the cause of reduced performance of the failing myocardium.

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