Progressive Loss of Myocardial ATP Due to a Loss of Total Purines During the Development of Heart Failure in Dogs

A Compensatory Role for the Parallel Loss of Creatine

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Background—Whether myocardial ATP content falls in heart failure is a long-standing and controversial issue. The mechanism(s) to explain any decrease in ATP content during heart failure have not been identified.

Methods and Results—Cardiac dysfunction, heart failure, and a prolonged steady state of heart failure were induced by chronic right ventricular pacing for 1 to 2 weeks, 3 to 4 weeks, and 7 to 9 weeks in dogs. Cardiac function and myocardial O₂ consumption (MV₀₂) were measured with the dogs in the conscious state. ATP, total purine, and creatine were measured in biopsy specimens obtained at each stage. ATP and the total purine pool progressively fell at rates of 0.12 and 0.15 nmol mg⁻¹ d⁻¹, despite an increase in MV₀₂. The rate of loss of creatine was 1.06 nmol mg⁻¹ d⁻¹, 7 times faster than the depletion of total purine.

Conclusions—(1) ATP contents progressively decreased during heart failure as a result of a loss of the total purine pool.

The loss of purines may be due to inhibition of de novo purine synthesis. (2) Loss of creatine is an early marker of heart failure and may serve as a compensatory mechanism minimizing the reduction of the total purine pool in the failing heart. (Circulation. 1999;100:2113-2118.)

Key Words: adenosine triphosphate ■ purine ■ creatine ■ oxygen ■ heart failure

ATP provides energy for contraction. ATP concentration in the normal heart is maintained constant, despite variations in cardiac performance, through balanced changes in the rate of ATP synthesis and utilization. Whether changes in ATP content occur and if so, whether they contribute to heart failure remains controversial. Some studies of failing human hearts have found decreased ATP content correlating with the extent of the impairment in cardiac function,¹ while others have reported normal ATP content.² Conflicting results have also been found from studies in animal models.³⁻⁵

One explanation for these apparently conflicting results is that the ATP content changes at various stages during the development of heart failure. Because of the difficulties inherent in conducting longitudinal studies of heart failure in both patients and animal models, this has not been tested. The mechanisms explaining the loss of ATP have not been identified.

The goals of the present study were, first, to determine whether and, if so, when ATP content is reduced in the failing heart. If the ATP content is decreased in the failing heart, our second goal was to identify the mechanism(s) explaining the loss of ATP. Because the purine pool must be preserved if a normal ATP content is to be maintained, we tested whether and, if so, when the purine pool is reduced in the failing heart.

The loss of purines could result either from an inhibition of de novo purine synthesis or failure of ATP synthesis pathways (primarily oxidative phosphorylation) to rephosphorylate ADP. To assess whether ADP and AMP increase in the failing heart (and thereby increase purine efflux), we also calculated the ADP and AMP contents. Finally, we examined the role of creatine (Cr) in maintaining the purine pool in the failing heart, because a decreased Cr could affect the concentrations of ADP (and secondarily AMP) through the creatine kinase (CK) reaction: PCr+ADP+H⁺ ↔ ATP+Cr, where PCr is phosphocreatine.

To address these goals, the canine pacing model was used. The dogs were paced for 1 to 2 weeks to induce subclinical cardiac dysfunction and for 3 to 4 weeks to develop overt heart failure. To create a state of chronic heart failure, the duration of pacing was extended another 4 to 5 weeks at a reduced pacing rate. In this way, we were able to study cardiac function and myocardial high-energy contents at 3 different stages during the development of heart failure as well as in the control state. At each time, we obtained biopsy specimens for measurement of tissue contents of ATP, its primary metabolites, and Cr. We also measured myocardial
O₂ consumption (MV O₂) in vivo to evaluate flux through oxidative phosphorylation.

Methods

Animal Preparation

Dogs (n=26) were chronically instrumented for assessment of hemodynamics and cardiac function. Briefly, dogs were instrumented with left ventricular (LV) pressure transducers (model P6, Konigsberg), aortic and coronary sinus catheters, ultrasonic dimension crystals across the LV cavity and the LV free wall, and transonic flow probes (Transonic Systems) on the left circumflex coronary artery. A screw-in-type pacing lead was attached to the right ventricular free wall, and left atrial pacing electrodes were also implanted. All wires and catheters were externalized. The dogs were allowed to recover completely for 2 to 3 weeks before experiments. Hemodynamics and cardiac function, including heart rate, mean arterial pressure, LV pressure and LV dP/dt, LV diameters and wall stress, and left circumflex coronary blood flow, were recorded with the dogs fully awake. Animals were maintained in accordance with the Guide for the Care and Use of Laboratory Animals (NIH publication No. 93-23, revised 1985).

Chronic Pacing-Induced Heart Failure

Congestive heart failure was induced by chronic rapid right ventricular (RV) pacing with a programmable pacemaker (Pace Medical). The experimental dogs were divided into four groups: control group (n=9), instrumented without pacing; 1- to 2-week pacing group (n=5), pacing at 240 bpm for 9±2 days to produce cardiac dysfunction without clinical signs of heart failure; 3- to 4-week pacing group (n=7), pacing at 240 bpm for 25±2 days to induce heart failure; and 7- to 9-week pacing group (n=6), pacing at 240 bpm for 3 to 4 weeks followed by pacing at 210 bpm for another 4 to 5 weeks for a total of 56±5 days to create and maintain chronic heart failure. Before the onset and at the end of the pacing protocol, hemodynamics and cardiac function were assessed (for all groups), and arterial and coronary sinus blood samples were collected (only for the 1- to 2-week and 3- to 4-week pacing groups). Myocardial O₂ extraction was calculated as the arterial and coronary sinus blood O₂ content difference, and MV O₂ was calculated as the product of O₂ extraction and mean coronary blood flow.

Biopsy and Analytical Assays

After the in vivo measurements were completed, the dogs were anesthetized with pentobarbital sodium (25 mg/kg) and ventilated with a respirator (Harvard), and the heart was exposed through a left thoracotomy. With a high-speed air turbine biopsy drill connected via a vacuum line to a bottle filled with liquid nitrogen, transmural biopsies (1 mm in diameter) were obtained from both LV and RV free walls and rapidly frozen (~1 second). Biopsy specimens were stored at -80°C.

Tissue concentrations of the primary nucleotides, nucleosides, and bases were measured by high-performance liquid chromatography (HPLC, Waters). Purines were eluted from a YMC ODS-AQ column, 4.6×150 mm at room temperature isocratically with 0.05 mol/L phosphate buffer (pH 6.0) at a flow rate of 0.8 mL/min and were analyzed at 254 nm. Aliquots of the homogenate taken before centrifugation were made alkaline and incubated overnight at 38°C to solubilize total protein for Lowry protein assay. Another set of aliquots was used for measurement of total Cr.

Data Analysis

LV fractional shortening (FS) was calculated as 100×(LVEDD – LVESD)/LVEDD, where LVEDD and LVESD denote the end-diastolic and end-systolic LV internal diameters. Wall stress (WS) was calculated by use of a cylindrical model as 1.36×(LVP×LVID)/2WT (g/cm²), where LVP is LV pressure, LVID is LV internal diameter, and WT is wall thickness. LVFS were measured at end diastole and end systole.

Interstitial edema and fibrosis have been reported for this model. In the present study, the dry/wet weight ratio (0.22±0.01) and the protein/wet weight ratio (0.13±0.01) were not different among groups, showing that the failing hearts paced according to this protocol have neither edema nor fibrosis. Substrate amounts were normalized by the amount of Lowry protein (primarily myocyte protein) to minimize any contributions of edema and fibrosis.

To calculate the cytosolic contents of ADP and AMP, we used the equilibrium expressions for creatine kinase and adenylate kinase. The equilibrium expression for the reaction PCr+ADP+H⁺ ↔ ATP+Cr is

\[ Keq = \frac{[ATP][\text{Free Cr}]}{[ADP][\text{PCr}][H^+]} = 1.66 \times 10^9 \]

and, rearranging,

\[ [\text{ADP}] = \frac{[ATP][\text{Free Cr}]}{[\text{PCr}][H^+]} \times 1.66 \times 10^9 \]

Henry et al. showed that PCr/ATP in the LV wall measured by 31P NMR spectroscopy was 2.25 in the normal dog and significantly lower, 1.98, in the canine model of heart failure after 3 weeks of rapid ventricular pacing. Thus, to calculate [ADP] for control and 3- to 4-week pacing groups, we used these values, our measured values for [ATP], and [total Cr] and made the reasonable assumption that the intracellular pH was 7.1. For the 1- to 2-week and 7- to 9-week pacing groups, we determined [PCr] using the ratio of PCr to Cr observed for the control and 3- to 4-week pacing groups (0.55). The equilibrium expression for the reaction 2ADP ↔ ATP+AMP is

\[ Keq = \frac{[\text{ATP}][\text{AMP}]}{[\text{ADP}]^2} = 1.05 \]

and, rearranging,

\[ [\text{AMP}] = \frac{[\text{ADP}]^2 \times 1.05}{[\text{ATP}]} \]

[AMP] was calculated by use of measured values of ATP and calculated values of ADP.

Statistical Analysis

Data are expressed as mean±SEM. For hemodynamic, cardiac function, and MV O₂ data, Student’s t test was used for paired comparisons. For the biochemistry data, 1-way factorial ANOVA and Tukey’s highly significant difference post hoc test for multiple comparisons. For the longitudinal changes in ATP and Cr and the sum of adenine nucleotides with pacing time, curve fitting and regression analysis were used. All statistical analyses used Statview (Brainpower, Calabasas). Significant changes were considered for P<0.05.

Results

Hemodynamics and Cardiac Function Measured in the Conscious State

Before the onset of pacing, hemodynamic and cardiac function parameters for each of the 3 pacing groups were not different from the control group (Table 1). Exertional dyspnea and ascites did not develop until after 2 to 3 weeks of pacing. Thus, there was cardiac dysfunction without overt clinical signs of heart failure in dogs with 1- to 2-week pacing. Dogs with 3- to 4-week pacing were in severe heart failure. Before the onset and at the end of the pacing protocol, hemodynamic and cardiac function were assessed (for all groups), and arterial and coronary sinus blood samples were collected (only for the 1- to 2-week and 3- to 4-week pacing groups). Myocardial O₂ extraction was calculated as the arterial and coronary sinus blood O₂ content difference, and MV O₂ was calculated as the product of O₂ extraction and mean coronary blood flow.

In the conscious state, heart rate and comparable decreases in mean arterial pressure, LV systolic pressure, and LV dP/dt after pacing in all 3 pacing groups. LVFS decreased in the 1- to 2-week pacing...
Progressive Decrease in ATP

Figure 1 (left) shows data for LV ATP content for each dog plotted against the duration of pacing. LV ATP content decreased monotonically with pacing time at a rate of 0.12 nmol · mg protein$^{-1}$ · d$^{-1}$. Table 2 shows these data arranged by group. Compared with the control group, the change in LV ATP in the 1- to 2-week pacing group was not significant, even though isovolumic and ejection phase indices in these dogs were lower. LV ATP content was 11% lower (P<0.05) in the 3- to 4-week pacing group and remained elevated in the 7- to 9-week pacing group (Table 1).

Progressive Decrease in Cr

Figure 2 shows a progressive decrease in LV Cr content with pacing time. Cr was reduced by 15% (P<0.05) in the 3- to 4-week pacing group and by 21% (P<0.05) in the 7- to 9-week pacing group. Figure 1 (middle) shows the data for LV TAN for each dog plotted against days of pacing. TAN decreased monotonically with pacing time. Regression analysis shows a linear relationship between TAN and ATP contents (Figure 1, right). The changes in RV TAN were similar to those in LV TAN, but the reduction occurred earlier (Table 2).

Tissue ADP and AMP contents were not significantly different among the control and the 3 pacing groups (Table 2). However, as observed for ATP and TAN, calculated cytosolic ADP and AMP contents progressively decreased (Table 3).

Progressive Depletion of Purines

To test whether the loss of ATP in the failing heart results from the loss of purines or whether the products of ATP degradation increased, thereby preserving the purine pool, we measured the primary adenine nucleotides, nucleosides, and nucleobases in biopsy samples from the 4 groups of dogs studied. The tissue contents of adenosine, inosine, and hypoxanthine were barely detectable in all 4 groups (data not shown). Because these metabolites were present in only trace amounts, the sum of the 3 nucleotides, ATP+ADP+AMP, closely approximates the size of the total adenine pool (TAN).

Analysis by groups revealed the same pattern for TAN as for ATP (Table 2). LV TAN was similar for the control group and the 1- to 2-week pacing group but was depleted by 15% (P<0.05) in the 3- to 4-week pacing group and by 21% (P<0.05) in the 7- to 9-week pacing group. Figure 1 (middle) shows the data for LV TAN for each dog plotted against days of pacing. TAN decreased monotonically with pacing time. Regression analysis shows a linear relationship between TAN and ATP contents (Figure 1, right). The changes in RV TAN were similar to those in LV TAN, but the reduction occurred earlier (Table 2).

Tissue ADP and AMP contents were not significantly different among the control and the 3 pacing groups (Table 2). However, as observed for ATP and TAN, calculated cytosolic ADP and AMP contents progressively decreased (Table 3).
The similar decreases in Cr content were also observed in the RV, but the reduction of Cr was more severe in the 1- to 2-week pacing group (29%, \( P<0.05 \)) (Table 2).

### ATP Synthesis Rate

To examine whether the reduced ATP content in the pacing-induced failing heart is due to lower capacity for oxidative phosphorylation, MV\(_2\)O\(_2\) was measured directly. Values for MV\(_2\)O\(_2\), coronary blood flow, arterial and coronary sinus blood O\(_2\) content, and O\(_2\) extraction in dogs with 1- to 2-week pacing and 3- to 4-week pacing are shown in Table 4. MV\(_2\)O\(_2\) was the same as for baseline in the 1- to 2-week pacing group and was 38±11% (\( P<0.05 \)) higher in dogs in the 3- to 4-week pacing group. The increase in MV\(_2\)O\(_2\) was accompanied by an increase in coronary blood flow.

### Discussion

#### Pacing-Induced Heart Failure in Dogs

In the pacing-induced heart failure model used here, animals develop progressive ventricular dilation with decreased myocardial contractility.\(^6^,\(^7\) This model has been used to study some biochemical alterations in the failing heart,\(^3^,\(^14\) but none of those studies achieved a chronic steady state of heart failure, performed a longitudinal analysis of pump function and biochemistry of ATP, or identified the mechanisms for ATP depletion during the development of heart failure. In the present study, animals were paced for different lengths of time and different rates to establish 4 distinct conditions, namely, control, cardiac dysfunction, heart failure, and chronic heart failure, allowing a longitudinal analysis of the biochemistry of ATP.

#### ATP Content

The results presented here for ATP content measured during the development of cardiac dysfunction and failure provide a likely explanation for the conflicting literature results on this subject. ATP content decreased monotonically with time of pacing at a rate of 0.35% of the total ATP pool per day. Thus, the reduction of ATP content is not large enough to be easily detected until heart failure is severe. Of note, the magnitude of the decrease in ATP in the severely failing dog heart observed here (≈20%) is similar to the decrease in ATP found for severely failing small-animal\(^13\) and human\(^16\) hearts.

The observation that ATP content is lower than normal in the severely failing heart requires reinterpretation of the PCr/ATP values measured by \(^{31}\)P NMR spectroscopy for the failing human heart.\(^17\) The significance of changes in this ratio has focused on decreases in PCr. Because ATP content also decreases, these changes in PCr have been underestimated by as much as 20%.

### Table 2. Myocardial Content of ATP Metabolites in Dogs With Pacing-Induced Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Control (n=9)</th>
<th>1–2-wk Pacing (n=5)</th>
<th>3–4-wk Pacing (n=4)</th>
<th>7–9-wk Pacing (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATP, nmol/mg protein</strong></td>
<td>34.2±0.9</td>
<td>33.6±1.0</td>
<td>32.8±0.8</td>
<td>30.3±0.9*</td>
</tr>
<tr>
<td><strong>ADP, nmol/mg protein</strong></td>
<td>6.9±0.8</td>
<td>6.0±0.7</td>
<td>4.5±0.4</td>
<td>4.7±0.5</td>
</tr>
<tr>
<td><strong>AMP, nmol/mg protein</strong></td>
<td>1.4±0.4</td>
<td>1.0±0.4</td>
<td>0.5±0.2</td>
<td>0.9±0.3</td>
</tr>
<tr>
<td><strong>TAN, nmol/mg protein</strong></td>
<td>42.3±1.4</td>
<td>40.6±1.6</td>
<td>37.8±1.0*</td>
<td>36.0±1.1*</td>
</tr>
<tr>
<td><strong>Cr, nmol/mg protein</strong></td>
<td>155±5</td>
<td>131±3*</td>
<td>112±5*</td>
<td>111±5†</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

\(^*P<0.05\) vs Control; \(^†P<0.05\) vs 1–2-wk pacing group; \(^‡P<0.05\) vs 3–4-wk pacing group.

### Table 3. LV Cr, PCr, ADP, and AMP Contents in Dogs With Pacing-Induced Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Control (n=9)</th>
<th>1–2-wk Pacing (n=5)</th>
<th>3–4-wk Pacing (n=4)</th>
<th>7–9-wk Pacing (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Free Cr, nmol/mg protein</strong></td>
<td>70±2</td>
<td>60±1*</td>
<td>50±2*</td>
<td>41±2†</td>
</tr>
<tr>
<td><strong>PCr, nmol/mg protein</strong></td>
<td>85±3</td>
<td>72±2*</td>
<td>61±3*</td>
<td>50±2*†</td>
</tr>
<tr>
<td><strong>ADP, nmol/mg protein</strong></td>
<td>0.22±0.01</td>
<td>0.21±0.01</td>
<td>0.19±0.01*</td>
<td>0.17±0.01†</td>
</tr>
<tr>
<td><strong>AMP, pmol/mg protein</strong></td>
<td>1.45±0.03</td>
<td>1.42±0.04</td>
<td>1.29±0.04*</td>
<td>1.16±0.04‡</td>
</tr>
<tr>
<td><strong>ATP/ADP ratio</strong></td>
<td>157</td>
<td>158</td>
<td>157</td>
<td>158</td>
</tr>
<tr>
<td><strong>ADP, nmol/mg protein</strong></td>
<td>0.22±0.01</td>
<td>0.30±0.01*</td>
<td>0.37±0.04†</td>
<td>0.44±0.02‡†</td>
</tr>
<tr>
<td><strong>AMP, pmol/mg protein</strong></td>
<td>1.45±0.03</td>
<td>2.8±0.2*</td>
<td>4.8±0.8†</td>
<td>7.5±0.6‡‡</td>
</tr>
<tr>
<td><strong>ATP/ADP ratio</strong></td>
<td>157</td>
<td>113*</td>
<td>82†</td>
<td>62††</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

\(^*P<0.05\) vs Control; \(^†P<0.05\) vs 1–2-wk pacing group; \(^‡P<0.05\) vs 3–4-wk pacing group.
Possible Mechanisms for the Mismatch Between ATP Synthesis and Degradation

A major result of our study is that the decrease in the TAN size closely parallels the loss in ATP content. The progressive depletion of TAN in the failing heart indicates that the rate of ATP synthesis fails to match the rate of ATP degradation. There are several ways this mismatch could occur. One way is failure to synthesize the purine ring via de novo pathways while a balance is maintained (although at different absolute rates) among the other pathways for ATP synthesis and utilization. Zimmer et al.19 measured the rate of de novo adenine synthesis in the normal beating mammalian (rat) heart in situ. If their value of 0.86 nmol·mg protein\(^{-1}\)·d\(^{-1}\) applies to the dog heart, then a reduction of only \(\approx 17\%\) in the rate of de novo purine synthesis would account for the loss of TAN observed here (0.15 nmol·mg protein\(^{-1}\)·d\(^{-1}\)). These observations merit further study.

Another mechanism that could explain the loss of purine independently of the rate of de novo purine synthesis is a failure of the primary pathways for ATP synthesis to meet increased demand caused by pacing tachycardia. Compared with control, MV\(\dot{O}\)\(_2\) was unchanged in the 1- to 2-week pacing group when the ATP content was close to normal but was 38% higher in the hearts with severe failure (3- to 4-week pacing group) when the ATP content was lower than for control. These data are consistent with those of others.19 –21 Importantly, these results indicate that the increase in MV\(\dot{O}\)\(_2\) was not sufficient to prevent purine loss.

Does Loss of Creatine Preserve the Purine Pool?

The critical step in evaluating whether the loss of purine is due primarily to failure of the ATP-synthesizing pathways to meet demand or to inhibition of de novo purine synthesis (or both) is assessment of whether cytosolic ADP and AMP levels are higher. It is important to point out that tissue ADP content obtained from HPLC measures the sum of the small cytosolic pool of ADP (20 to 100 \(\mu\)mol/L) and the large pool of ADP released from proteins such as actin (0.5 to 1 mmol/L). Thus, increases in cytosolic ADP content cannot be (and were not) detected against this large background of protein-bound ADP. Changes in cytosolic ADP content are best estimated from the CK equilibrium expression.

It is clear from the CK equilibrium expression that cytosolic [ADP] would increase if the [PCr]/[ATP] fell and the total creatine pool remained unchanged. Free [ADP] would nearly double in the two heart failure groups if the total Cr content remained at the normal level (Table 3). Under these conditions, the pathway for ATP degradation would be stimulated, and purine would be lost from the cells. This is the typical scenario that accounts for loss of purines in ischemia and hypoxia.22 But, as reported here, a different metabolic pattern occurs in this model of heart failure. The Cr pool is not preserved but rather is progressively depleted in the failing heart at a rate 7 times faster than for purines. As a result, the ratio of PCr to Cr is nearly normal.

Maintaining a normal PCr/Cr ratio has two important correlates. The first is that [ADP] is maintained close to normal levels (Table 3). As a consequence, the loss of the purine pool would be minimized. It is important to emphasize that the loss of purine observed in the present study would be even greater if the Cr pool were not decreased.

The second correlate is that ATP/ADP is maintained at near normal levels, despite decreased [ATP] (Table 3). Because ATP/ADP is the critical ratio driving all of the ATPase reactions in the cell, the preservation of ATP/ADP suggests that the loss of Cr may be adaptive. Although the loss of Cr reduces the capacity of the CK reaction for ATP resynthesis,15 the analysis presented here shows that the loss of Cr also minimizes the reduction of the purine pool, maintaining a nearly normal ATP/ADP. Although supporting high workload is important, maintaining nearly normal PCr/Cr and ATP/ADP ratios is more important, indeed essential, for cell survival.

The results of this analysis are consistent with the following model of energetics in the failing heart: (1) loss of Cr plays a quantitatively important role minimizing the loss of purine pool and maintaining a normal ATP/ADP ratio; (2) the increase in MV\(\dot{O}\)\(_2\) partially compensates for the increased

**TABLE 4. MV\(\dot{O}\)\(_2\) in Dogs With Pacing-Induced Heart Failure**

<table>
<thead>
<tr>
<th></th>
<th>1–2-wk Pacing (n=5)</th>
<th>3–4-wk Pacing (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Pacing</td>
<td>After Pacing</td>
</tr>
<tr>
<td>Coronary blood flow, mL/min</td>
<td>29.3±3.2</td>
<td>28.1±2.9</td>
</tr>
<tr>
<td>Arterial (O_2) content, mL (O_2/100\ mL)</td>
<td>14.3±1.0</td>
<td>15.0±1.4</td>
</tr>
<tr>
<td>Venous (O_2) content, mL (O_2/100\ mL)</td>
<td>4.0±0.7</td>
<td>3.1±0.5</td>
</tr>
<tr>
<td>(O_2) extraction, mL (O_2/100\ mL)</td>
<td>10.3±0.9</td>
<td>11.9±1.2</td>
</tr>
<tr>
<td>(O_2) consumption, mL (O_2/min)</td>
<td>3.1±0.4</td>
<td>3.4±0.6</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

\*P<0.05 vs before pacing.
energy demand, but the increase is not sufficient to salvage ADP levels; and (3) de novo purine synthesis is likely to be inhibited in the failing heart and could account for the loss of purine in the failing heart.

Conclusions
There is a progressive decrease in ATP and the total purine pool in the failing heart. Thus, despite increased MV˙O₂, the pathways for ATP synthesis fail to meet the metabolic demands of the failing heart, raising the possibility that de novo purine synthesis is inhibited. Loss of creatine is also progressive and occurred at a rate 7 times faster than loss of ATP. Thus, even at the time when ATP content has not yet fallen substantially from control levels, there is a decrease in the Cr pool. These results suggest that loss of Cr could be a sensitive and early marker of cardiac dysfunction associated with heart failure. We suggest that the primary consequence of the loss of Cr may be a compensatory mechanism minimizing the reduction of the adenine nucleotide pool in the failing heart.

Acknowledgments
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References
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