Interstitial purine metabolites in hearts with LV remodeling

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Congestive heart failure (CHF) is associated with abnormal myocardial energy metabolism (9, 12, 20, 31, 44). The mechanisms of this abnormality and the contribution to the evolution from compensated cardiac hypertrophy to CHF are not known (9, 12). The myocardial ATP concentration is significantly decreased in failing hearts (31) or in hearts with postmyocardial infarction (MI) left ventricular (LV) remodeling (44), which may be related to the progressive loss of the myocardial total adenine nucleotide pool. The levels of interstitial purine metabolites (IPM) under catecholamine stimulation or during regional myocardial ischemia have been demonstrated as sensitive markers of tissue ATP depletion (7, 8, 36).

Previous studies have demonstrated that cardiac hypertrophy is accompanied by abnormal myocardial energetics with a decreased myocardial phosphocreatine (PCr)-to-ATP ratio (PCr/ATP) and increased myocardial free ADP level (17, 19, 27, 35, 39–44). The increase of myocardial free ADP initiates adenylate kinase (myokinase) activation, which catalyzes the transfer of a phosphoryl group between two ADP to form one AMP and one ATP (6, 11, 14, 30, 34). The increased AMP induces the conversion of AMP to adenosine (30). Adenosine can cross the cell membrane and get into the interstitial space, where it is further degraded to inosine and hypoxanthine and leaves the heart with myocardial perfusion (16). The resulting loss of TAN from adenosine diffusion leads to a high demand of the de novo synthesis pathway. This loss of TAN results in the reduction of ATP concentration because the de novo synthesis of the adenine nucleotide is a slow and energy costly process, where inosine monophosphate (IMP) is produced from ribose-5-phosphate, which utilizes six high-energy phosphate bonds (16). In the postischemic myocardium of the dog heart, it was found that the recovery process of the TAN pool takes a few days to complete (11, 32, 34). In dogs with rapid pacing-induced CHF, Shen et al. (31) found that the decreased myocardial ATP concentration is related to the reduction of myocardial TAN (31). The underlying mechanisms of this progressive depletion of the TAN pool during the development of CHF are not known. We hypothesized that if the reduction of myocardial ATP concentration of the remodeling ventricle is caused by a reduction of the TAN pool, then the levels of interstitial purine metabolites (IPM) in the interstitial fluid should be significantly increased in these hearts. Using a rat model of post-MI LV remodeling and the cardiac microdialysis method, we found that the level of IPM was significantly increased in myocardium remote from the LV infarction both at baseline and during isoproterenol (Iso) infusion. These results provide direct evidence to support the hypothesis that the depletion of the TAN pool is significantly greater in hearts with post-MI LV remodeling, which could cause the reduction of the steady-state myocardial ATP concentration in the dysfunctional LV (19, 31, 38, 40, 41, 44). These changes may contribute to the progression of cardiac hypertrophy to chronic heart failure.

METHODS

Animal Model

The experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and by the regional ethical committee for laboratory animal experiments.

Male Wistar rats (n = 53), weighing 250–280 g, underwent either left coronary artery ligation (MI group, n = 40) or sham operation (sham group, n = 13). MI was produced by left coronary artery ligation or during regional myocardial ischemia have been demonstrated as sensitive markers of tissue ATP depletion (7, 8, 36).

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ligation by a method described previously (24). Briefly, animals were
anesthetized with ketamine hydrochloride (20 mg/kg ip), intubated,
and mechanically ventilated with room air. A left thoracotomy
through the fourth intercostal space was performed, and the pericar-
dium was removed. The heart was exteriorized by putting pressure on
the right hemithorax, and the left coronary artery was occluded with
a 6.0-silk suture 1 to 2 mm below the left atrial appendage. Successful
occlusion was confirmed by pallor of the anterior wall of the LV and
ST segment elevation on ECG. The sham group underwent an iden-
tical myocardial ligation without coronary artery ligation. All surviving rats
between 21 and 24 days after surgery were included in the study. The
rats were anesthetized with pentobarbital sodium (50 mg/kg ip).
Endotracheal tubes were placed, and the lungs were ventilated with
room air (1.2 ml/100 g body wt, 50–60 strokes/min). The right jugular
vein and femoral artery were cannulated for drug administration and
monitoring of blood pressure (BP), respectively. The chest was
opened, and a 2.5-mm electromagnetic flow probe (Transonic Sys-
tems; Ithaca, NY) was placed around the ascending aorta. Hemody-
amic measurements, including heart rate (HR), mean arterial BP, and
cardiac output (CO), were continuously recorded.

To examine whether a significant LV contractile dysfunction occurred
in hearts with LV remodeling, LV pressure were measured in a
separate group of eight animals with post-MI LV remodeling with a
pressure transducer placed in the LV, and results were compared with
five sham-operated normal animals.

Cardiac Microdialysis Techniques and Experimental Protocol

A microdialysis probe was implanted into the LV myocardium remote from the LV scar in the MI group and into a nearly similar area of
the myocardium in the sham group. Microdialysis probes were con-
structed with a single dialysis fiber (Cordis Dow; Brussels, Bel-
gium; 0.25 mm outer diameter, molecular weight cutoff 5,000). Each
end of the fiber was inserted into outflow and inflow silicon tubes and
sealed in place with cyanoacrylic glue. The dialysis fiber length was
6–8 mm and varied depending on the size of the infarction. The inflow
silicon tube was connected to a glass syringe of a perfusion pump
(CMA 100, Carnegie Medicine). After implantation, the microdialysis
probe was perfused with Ringer solution [containing (in mM) 147
NaCl, 4.0 KCl, and 2.3 CaCl₂] at a rate of 3.0 μl/min. Dialysate
sample collection was started 60 min after the probe implantation.
The starting infusion rate of ISO was 0.28 μg·kg⁻¹·min⁻¹ iv. The rate of
infusion increased 10-fold every 15 min during the following 1 h.
Dialysate samples were collected every 15 min at 30 min before, 60
min during, and 30 min after the end of ISO infusion.

LV Infarct Size and LV Volume

At the end of the hemodynamic experiments and the sample collect-
ion, the hearts were arrested by perfusion of ice-cold saturated
KCl through the jugular vein, excised, and placed on the left atrial appendage. The right ventricle was excised, the LV was
opened, and a 2.5-mm electromagnetic
flow probe was inserted into outflow and inflow silicon tubes and
sealed in place with cyanoacrylic glue. The dialysis fiber length was
6–8 mm and varied depending on the size of the infarction. The inflow
dsion rate 1 ml/min. The concen-
trations of inosine, hypoxanthine, xanthine, and UA were determined
with a mobile phase of 50 mM KH₂PO₄, 2.1
mM particles (ESA). The concentration of adenosine was determined with a mobile phase of 50 mM KH₂PO₄, 2.1
mM sodium octane sulfonate, 2.4 mM sodium hexane sulfonate, and
15% (vol) methanol (pH 4.40) at a flow rate 1 ml/min. The concen-
trations of inosine, hypoxanthine, xanthine, and UA were determined
with a mobile phase of the same content but without methanol (pH
2.35). The absolute detection limit (signal-to-noise ration: 3:1) was
calculated as 1 pmol/injection for adenosine and as 1.5–2.5 pmol/
injection for its metabolites.

Statistical Analysis

All values are presented as means ± SE. Data were analyzed with
one-way ANOVA for repeated measurements. The unpaired t-test
was used for the comparison of data between groups. A value of P < 0.05
was required for significance.

RESULTS

Mortality and Exclusions From the Study

Twenty-six of the initially included fifty-three rats died before the
experiments (23 in the MI group and 3 in the sham group). Thirteen deaths occurred within the first day after the
coronary artery ligation, and another ten animals died after
24 h. All other deaths were between 15 and 23 days after
surgery. Autopsy revealed extensive MI and signs of CHF. Three animals died within the first 24 h in the sham group.
Four rats were excluded because the infarct size was <15% of
the LV. Two animals in the MI group died during the ISO
infusion. Two animals in the MI group were excluded from the
study due to a large infarct size (>45% of the LV) and wrong
position of the microdialysis flow probe. The remaining 19
rats, 9 in the MI group and 10 in the sham group, were included in
the cardiac microdialysis study (Table 1). To examine
whether a significant LV contractile dysfunction occurred in
hearts with LV remodeling, LV pressure was measured in a
separate group of eight animals with post-MI LV remodeling
(3 of which died within the first 24 h), and the results were
compared with five sham-operated normal animals (Table 2).

Body Weight, LV Weight, and Infarct Size

No significant changes in body weight were observed in the
MI group compared with the sham group (286 ± 11 vs. 294 ±
14 g, P < 0.05). LV mass in the MI group was not significantly
higher than than in the sham group (data not shown). LV
volume in the MI group was larger (2.2 ± 0.2 ml/kg) compared
with the corresponding value in the sham group (1.3 ± 0.2
ml/kg, P < 0.01). Mean infarct size was 28 ± 4%.

Baseline Hemodynamic Data and Steady-State
IPM Concentrations

The baseline hemodynamic data and steady-state IPM con-
centrations are summarized in Table 1. Under basal conditions,
the HR, CO, and mean arterial BP were not significantly different
between the two groups (Table 1; P = not significant). In
hearts with post-MI LV remodeling, the steady-state concentra-
tions of adenosine, xanthine, and UA were increased signif-
ificantly (each P < 0.05; Table 1).
LV Contractile Function

LV contractile function of a separate group of five animals with MI versus five sham-operated normal animals are summarized in Table 2. The LV end-diastolic pressure was significantly increased in hearts with MI (P < 0.05), which was accompanied by a significant decrease of the first derivative of LV pressure (P < 0.05). These data demonstrate a significant decreased LV contractile performance in the post-MI LV remodeling group.

Time-Course Hemodynamic Data

Figure 1 illustrates the HR, CO, and mean aortic BP before, during, and after the Iso infusion. There were no significant differences between the two groups in hemodynamics before the onset of the Iso infusion. HR did not significantly change in the both groups during the Iso infusion, and there were no other differences between the groups at any time point (Fig. 1A). At the highest dose of the Iso infusion and 30 min after the cessation of infusion, higher levels of the rate-pressure product (RPP) were observed in the sham group compared with the MI group (data not shown). Iso induced an increase CO in the sham group only at the lowest rate of infusion but had no effect at higher infusion rates. CO in the MI group did not change throughout the experiment (Fig. 1C). Iso in increasing doses in both groups induced a decrease of BP, which persisted until the end of the experiment. At the highest dose of the Iso infusion and 30 min after the cessation of the infusion, higher levels of BP (P < 0.05) were observed in the sham group compared with the MI group (Fig. 1B).

Time-Course Myocardial Dialysate Purine Metabolite Levels

The temporal profile of dialysate adenosine levels are shown in Fig. 2A. The baseline adenosine levels were not different between the two groups. During Iso infusion, adenosine levels increased significantly in both groups (P < 0.05), which was significantly greater in the MI group (Table 1 and Fig. 2A).

Table 2. LV contractile function of animals with postinfarction LV remodeling compared with sham-operated normal animals

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>LV dP/dt, mmHg/s</th>
<th>LV End-Diastolic Pressure, mmHg</th>
<th>Infarct Size, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham operation</td>
<td>5</td>
<td>7.6±1.2</td>
<td>6±3</td>
<td></td>
</tr>
<tr>
<td>LV remodeling</td>
<td>5</td>
<td>4.1±1.4*</td>
<td>18±5*</td>
<td>31±4*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of animals. LV dP/dt, first derivative of LV pressure. *P < 0.05 vs. sham operation group.

Adenosine levels returned to near-baseline levels in both groups after 30 min after the cessation of the Iso infusion. The sum of dialysate adenosine levels during the Iso infusion was significantly higher (P < 0.05) in the MI group than in the sham group (Fig. 2B). The temporal profile of dialysate xanthine levels were shown in Fig. 3, A and B. These metabolites increased significantly (P < 0.05) in both groups of animals during the Iso infusion and remained elevated after the cessation of the Iso infusion.

The temporal profile of the dialysate xanthine level is shown in Fig. 4A. The xanthine level increased significantly during the Iso infusion in both groups (P < 0.05) and tended to be higher in the MI group (P < 0.05; Table 1). The total sum of dialysate xanthine levels was significantly higher (P < 0.05) in the MI group compared with the sham group during and after the cessation of the Iso infusion (Fig. 4B). Figure 5 illustrates the temporal profile of dialysate UA level changes. The baseline UA level was fourfold greater in the MI group (18.9 ± 3.4 μM/L) compared with the sham group (4.6 ± 0.7 μM/L, P < 0.01). During Iso infusion, the UA levels increased significantly in both groups and tended to increase more in the MI group (Fig. 5; P < 0.01). Compared with baseline, the UA levels were increased roughly 400% (Fig. 5) and remained elevated after the discontinuation of Iso infusion.

During the first 30 min of the Iso infusion, the most rapid increase levels of IPM except UA were noted. After this time, the levels were relatively stable through the end of the experiment.

DISCUSSION

The major findings of the present study are that the levels of IPM in myocardium remote from the LV scar both at baseline and during Iso administration were significantly higher in the MI group than in the sham group. These results provide support to the hypothesis that the loss of the TAN pool is significantly greater in hearts with cardiac hypertrophy. These changes may contribute to the decreased myocardial ATP concentration in hypertrophied and failing hearts.

Animal Model

The severity of LV hypertrophy and the rate of development of CHF are proportional to the infarct size (23). Our data showing an increase in LV geometry and decreases of cardiac function are in accordance with previously published data (22, 25, 26, 37).

Cardiac Microdialysis

Van Wylen et al. (36) established cardiac microdialysis as a reliable method to directly measure the purine metabolites.
during myocardial ischemia or in response to catecholamine stimulation. Headrick (7), using a rat model, demonstrated that the basal dialysate adenosine level was 0.10 \( \pm \) 0.01 \( \mu M \) and with epinephrine infusion was 3.2 and 8.0 \( \mu g \cdot kg^{-1} \cdot min^{-1} \), causing increases in the RPP by 72% and 157%, respectively. This RPP increase was associated with an increase of dialysate adenosine levels to 0.26 \( \pm \) 0.04 and 0.65 \( \pm \) 0.11 \( \mu M \) (7), therefore supporting the idea that cardiac interstitial adenosine levels increase in response to catecholamine stimulation dose dependently. A further study by Headrick et al. (8) using a similar infusion rate of epinephrine also demonstrated that the increased myocardial free ADP level (as indicated by the decrease of PCr/ATP) was accompanied by an increased in the dialysate adenosine level. This earlier work is further supported by the present study, as a graded Iso infusion resulted in significant higher dialysate adenosine levels in the MI group (\( P < 0.05 \); Fig. 2B) as a result of the loss in the TAN store.

Myocardial High-Energy Phosphate Metabolism During Catecholamine Stimulation

In the normal heart, the myocardial oxidative phosphorylation (OXHPOS) regulation remains constant over moderate increases of workload (RPP up to \( \sim 35,000 \) mmHg-beats-min\(^{-1} \)) (1, 13, 40). At higher cardiac workloads (RPP \( > 45,000 \) mmHg-beats-min\(^{-1} \)), several investigators observed that myocardial...
dial PCr levels fell and calculated ADP levels rose. These changes were associated with the appearance of Pi and some loss of ATP (17, 39). With the recent use of 1H magnetic resonance spectroscopy to examine the myoglobin oxygen saturation, it was found that these myocardial high-energy phosphate changes that occurred during high-dose catecholamine stimulation were independent from myocardial ischemia (43). Using an experimental system in which the oxygen supply was a strictly controlled variable, Stumpe et al. (33) found that the critical PO2 was 3 mmHg based on the ATP decrease and adenosine increase. In the rat heart in situ, Headrick et al. (8) demonstrated that epinephrine infusion (0.9 μg·kg⁻¹·min⁻¹) intravenously (i.v.) produced an increase of RPP by twofold that was accompanied by a significant decrease of PCr/ATP and a threefold increase of myocardial free ADP. The increase of epinephrine infusion to 2.8 μg·kg⁻¹·min⁻¹ further increased the RPP to 2.7-fold and elevated ADP more than 4-fold (8). These data suggest that in the in vivo heart at high cardiac work states, the myocardial free ADP level is significantly increased, which is accompanied by increased adenosine release. This increase of the myocardial free ADP level is independent from myocardial ischemia but may reflect a different metabolic setpoint of mitochondrialOXPHOS compared with basal cardiac work states.

Increase of Myocardial Free ADP and Reduction of ATP Concentrations

ATP concentration is significantly decreased in large animal models of end-stage CHF with clinical evidence of water retention (ascites) (31, 44). However, decreases in myocardial ATP concentration were not reported in some studies using small animal models of CHF. This discrepancy is most likely due to the fact that the experiments were done at different phases of CHF. The phase of clinical end-stage CHF is very rapid, and it is sometimes difficult to examine the animals at this time point of CHF. In a pig model of CHF, we examined animals at the clinical end stage of CHF. Once cyanosis or an increase of respiration rate occurred, the animals were terminally examined immediately, regardless of the time of the day. This timing may not be possible at other institutions or with other animal models of CHF.

The reasons for the depressed level of ATP in remodeled hearts are not known. Repetitive episodes of ischemia can cause a persistent depression of ATP levels, and this could apply to the subendocardium of CHF hearts in which the coronary reserve is impaired (41). However, no such abnormality was observed (19). An alternative possibility is that the
higher ADP levels in the remodeled hearts enhanced ATP catabolism via myokinase (7) and subsequent degradative reactions (31). In the myocyte, the mechanism that controls the set point of steady-state ATP levels is unclear, but it must reflect a balance between adenine nucleotide synthesis and degradation. If degradative reaction rates are even slightly enhanced in the absence of a compensatory increase in nucleotide synthetic rates, the net result could be a lower equilibrium for steady-state ATP levels. In principle, the ATP production rate should contribute to the steady-state myocardial ATP concentration. However, in the in vivo heart, this equation is complicated by the high reserve capacity of mitochondrial ATPase and the multiple regulations of the cascade ATP production pathway.

Reduced ATP production. In the heart, the contractile chemical energy ATP is mainly produced in mitochondria. Mitochondrial ATP synthase (mtATPase), which is embedded in the mitochondrial inner membrane, drives ATP synthesis using energy generated from the electrochemical proton gradient across the inner mitochondrial membrane (5, 15). The protein levels of mtATPase F1F0 subunits were all lower in failing versus normal hearts, and the decreases were significantly related to the degree of reduction of the myocardial steady-state high-energy phosphate levels: PCr and ATP (15, 38). This implies that reductions of ATPase protein expression are associated with the degree of reduced ATP concentration (15, 38). A decrease of the β-F1-ATPase activity or an increase of its apparent Km value with respect to ADP could require an increase of cytosolic ATP and ADP levels to maintain a given rate of ATP synthesis. However, because of the presence of endogenous inhibitors, including inhibition factor 1, ATP synthetic activity cannot be directly equated with the myocardial F1F0-ATPase content. Because of the presence of baseline inhibition, the protein content cannot be directly equated with in vivo enzyme activity. However, the decreased protein expression could limit the maximum ATP synthesis rates achievable during state of an maximum increased ATP demand/utilization, which could result in a reduction of ATP concentration.

Decrease of ATP transfer. Mitochondrial creatine kinase (CK) and the β-subunit of F1F0-ATPase, respectively, facilitate ADP/ATP exchange across the inner mitochondrial membrane and catalyze the phosphorylation of ADP to form ATP. The specific intracellular localization of CK isoforms serves to maintain low cytosolic ATP levels in the normal heart. In post-MI LV remodeled hearts and in failing hearts, a fetal shift of myocardial CK expression has been reported, with a decrease in the MM isoform and increases in the MB and BB isoforms (9, 19, 38). Similar findings were observed in a canine model of LV hypertrophy produced by ascending aortic banding. Although the mechanism and functional consequences of these CK isoform shifts in the hypertrophied and failing heart are unclear, previous studies have demonstrated that decreases of CK activity have the potential to affect myocardial ATP concentration and performance. Mitochondrial CK is located in association with adenine nucleotide translocase, where it catalyzes the transfer of a phosphoryl from ATP to creatine, forming PCr. In this fashion, mitochondrial CK can maintain high local levels of ADP for ATP synthase but low mean cytosolic ADP values. Conversely, CK-MM, located adjacent to myosin ATPase, can catalyze phosphoryl transfer from PCr to ADP formed during contraction, thereby maintaining high ATP levels to drive contraction and also acting to maintain low mean cytosolic levels of ADP. The reexpression of the fetal gene program with increased CK-B and decreased CK-M and mitochondrial CK in the post-MI heart is associated with higher cytosolic levels of ADP for any rate of ATP synthesis. Therefore, it is possible that alterations of CK isoform expression could have contributed to the decreased myocardial ATP level in failing hearts.

Increased ATP utilization. One primary indicator of heart failure is a significantly increased LV volume/end-diastolic pressure (Table 2). A dilated ventricle by necessity requires significantly more ATP to support itself in accordance with Laplace’s Law.

Reduction of the TAN pool. During the steady state of metabolic activity of normal myocardium, the balance of the continual loss of myocardial purine nucleotides is mainly via the salvage pathways by which one enzyme convert a purine nucleotide or base to another nucleotide (16). However, in postischemic myocardium, the reestablishment of the normal TAN pool is thought to occur via a de novo pathway by which purine nucleotides are synthesized from nonpurine precursors (11, 16, 32, 34). In diseased myocardium, the increase of myocardial free ADP initiates adenylate kinase (myokinase) activation, which catalyzes the transfer of a phosphoryl group between two ADP to form one AMP and one ATP (8, 16). The resulting increased AMP would favor the conversion of AMP to adenosine (33), finally leading to myocyte adenosine deaminase degradation of adenosine to inosine (2, 32). Unlike adenosine nucleotides, which do not cross the sarcolemma, adenosine and inosine can cross the cell membrane to the interstitial space, where they are degraded to hypoxanthine, xanthine, and UA (16, 18, 31) and subsequently eliminated from the heart via myocardial blood flow. This depletion of the TAN pool results in a reduction of ATP as the resynthesis of adenosine nucleotides is a slow and energy costly process. The resynthesis of adenosine
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REFERENCES

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Increased IPM and Increased Reactive Oxygen Species

The last purine metabolite, UA, is formed by the enzyme xanthine oxidase (XO) (10). Data from the present study indicate that dialysate xanthine and UA in hearts with post-MI LV remodeling were significantly increased, which indicates that XO activity may also be increased. Ekelund et al. (4) found that XO activity was fourfold increased in failing hearts compared with controls. It is interesting to note that XO forms superoxide radical in the terminal step of the purine metabolism that has been proposed as a pathogenic factor in the development of CHF (5). More recently, data from both experimental animal models as well as clinical observations indicate that the XO inhibitor allopurinol decreases the myocardial energy demands and at the same time increases cardiac contractility in failing hearts but not in normal hearts (3, 4). This observation supports the hypothesis that superoxide radical is increased in myocardium of failing hearts, which may be caused by the abnormal protein expression of the enzymes of mitochondrial oxidative phosphorylation regulation (OXPHOS) (15, 38).

In conclusion, failing hearts are associated with an increased level of myocardial total interstitial purine metabolites both at baseline and during Iso infusion, which may be triggered by the alterations in the mitochondrial OXPHOS set point with a manifestation of increased cytosolic free ADP. This abnormality may contribute to the reduction of myocardial ATP concentration in failing hearts, which, in turn, could contribute to the progression of cardiac hypertrophy to chronic heart failure.

GRANTS

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