

# Diastolic Dysfunction in Hypertensive Heart Disease Is Associated With Altered Myocardial Metabolism

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**Background**—Hypertension is an important clinical problem and is often accompanied by left ventricular (LV) hypertrophy and dysfunction. Whether the myocardial high-energy phosphate (HEP) metabolism is altered in human hypertensive heart disease and whether this is associated with LV dysfunction is not known.

**Methods and Results**—Eleven patients with hypertension and 13 age-matched healthy subjects were studied with magnetic resonance imaging at rest and with phosphorus-31 magnetic resonance spectroscopy at rest and during high-dose atropine-dobutamine stress. Hypertensive patients showed higher LV mass ( $98 \pm 28$  g/m<sup>2</sup>) than healthy control subjects ( $73 \pm 13$  g/m<sup>2</sup>,  $P < 0.01$ ). LV filling was impaired in patients, reflected by a decreased peak rate of wall thinning (PRWThn), E/A ratio, early peak filling rate, and early deceleration peak (all  $P < 0.05$ ), whereas systolic function was still normal. The myocardial phosphocreatine (PCr)/ATP ratio determined in patients at rest ( $1.20 \pm 0.18$ ) and during stress ( $0.95 \pm 0.25$ ) was lower than corresponding values obtained from healthy control subjects at rest ( $1.39 \pm 0.17$ ,  $P < 0.05$ ) and during stress ( $1.16 \pm 0.18$ ,  $P < 0.05$ ). The PCr/ATP ratio correlated significantly with PRWThn ( $r = -0.55$ ,  $P < 0.01$ ), early deceleration peak ( $r = -0.56$ ,  $P < 0.01$ ), and with the rate-pressure product ( $r = -0.53$ ,  $P < 0.001$ ).

**Conclusions**—Myocardial HEP metabolism is altered in patients with hypertensive heart disease. In addition, there is an association between impaired LV diastolic function and altered myocardial HEP metabolism in humans. The level of myocardial PCr/ATP is most likely determined by the level of cardiac work load. (*Circulation*. 1999;99:2261-2267.)

**Key Words:** magnetic resonance imaging ■ spectroscopy ■ hypertension ■ diastole ■ stress

High blood pressure has a high prevalence in the general population and is one of the major risk factors for coronary heart disease.<sup>1</sup> Early detection of changes in cardiac performance, before irreversible damage to the heart has occurred, can contribute substantially to a further decline in hypertension-related death.<sup>1</sup>

Previous echocardiographic and radionuclide studies have shown impaired diastolic heart function in hypertension, even in the absence of left ventricular (LV) hypertrophy (LVH),<sup>2-8</sup> whereas systolic function is still preserved.<sup>2-4,7,8</sup> Animal studies have shown that myocardial high-energy phosphate (HEP) metabolism is altered in hypertensive heart disease, in particular when LV mass is increased.<sup>9-12</sup> Experimental work has suggested that there is a relation between diastolic dysfunction and altered myocardial creatine kinase kinetics.<sup>10</sup>

Magnetic resonance (MR) imaging is a highly reliable technique for assessment of LV dimensions and systolic and diastolic function.<sup>13,14</sup> Phosphorus-31 (<sup>31</sup>P) MR spectroscopy is a noninvasive, reproducible method to study myocardial HEP metabolism in vivo.<sup>15-18</sup> The combination of functional and metabolic evaluation of the human heart in a single MR examination may ultimately provide a sensitive tool for early

detection of changes in cardiac performance and myocardial viability.

A previous study<sup>19</sup> showed that myocardial HEP metabolism of the normal human heart is altered at high work loads. A decrease in myocardial PCr/ATP was found when normal hearts were stressed severely on infusion of atropine-dobutamine (A-D). Acquisition of <sup>31</sup>P-MR spectra during high-dose A-D infusion in patients with hypertensive heart disease may provide new pathophysiological insights in the disease.

Accordingly, the purpose of the present study was 2-fold: first, to test the hypothesis that myocardial HEP metabolism is altered in hypertensive heart disease and that this is associated with disturbances in cardiac function, especially diastolic dysfunction, and second, to determine the effects of severe pharmacological stress testing on myocardial HEP metabolism in patients with hypertensive heart disease.

## Methods

### Study Subjects

Eleven male patients with repeated increased systolic blood pressure (SBP) measurements ( $\geq 140$  mm Hg) and/or diastolic blood pressure (DBP) readings ( $\geq 90$  mm Hg)<sup>1</sup> were included in the present study.

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**TABLE 1. Hemodynamic and Metabolic Data at Rest and During A-D Stress**

Parameter	Rest	Stress	% Change (Rest→Stress)
Heart rate, bpm			
Control subjects	63±9	147±11§	142±29
Patients	67±8	142±13§	116±34
SBP, mm Hg			
Control subjects	121±10	152±15§	26±14
Patients	159±22†	168±25	6±13†
DBP, mm Hg			
Control subjects	73±5	74±11	2±13
Patients	89±7†	86±12*	-3±12
RPP, mm Hg×bpm×10 <sup>-2</sup>			
Control subjects	77±12	224±28§	204±54
Patients	107±27†	239±44§	132±57†
PCr/ATP			
Control subjects	1.39±0.17	1.16±0.18§	-16±12
Patients	1.20±0.18*	0.95±0.25*‡	-21±18
P <sub>i</sub> -e			
Control subjects	1.43±0.26	1.92±0.39§	35±23
Patients	1.76±0.45*	2.41±0.72§	47±46

Note that values for myocardial PCr/ATP and P<sub>i</sub>-e determined at rest in patients are similar to values obtained in healthy subjects during A-D infusion. Control subjects vs patients; \**P*<0.05, †*P*<0.01. Rest vs stress, ‡*P*<0.01.

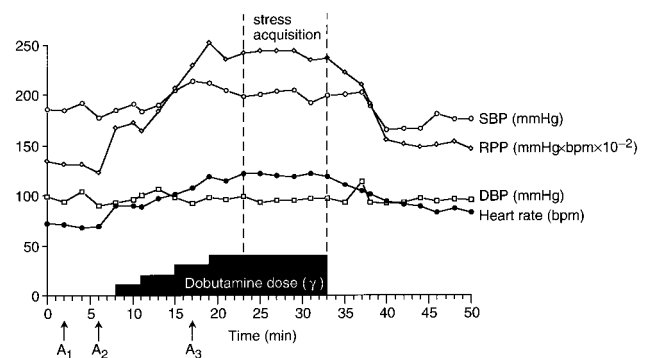
Their average untreated SBP and DBP were 179±27 mm Hg and 107±10 mm Hg, respectively, classified as stage III hypertension according to the Fifth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.<sup>1</sup> Patients were treated with a variety of antihypertensive drugs, mainly ACE inhibitors, calcium antagonists, and β-blockers. However, their blood pressures had not yet normalized at the time of inclusion in the present study (Table 1). Patients were gradually withdrawn from β-blockers 2 weeks before the current examinations. Patients with a history of coronary artery disease (CAD), cerebrovascular disease, malignant hypertension, renal insufficiency, or diabetes mellitus were excluded.

Thirteen male control subjects were normal at clinical examination, showed a normal ECG at rest, were not obese (see below), normotensive (Table 1), without a history of cardiovascular disease, and without any complaints. The control subjects had no ECG-based evidence of ischemia during bicycle exercise testing (3.0±1.2-fold increase in rate-pressure product; RPP) and were without anginal complaints.<sup>15</sup> Their posttest likelihood for CAD was <2.5%.<sup>20</sup>

The age of healthy subjects (53±7 years) and patients (59±10 years) was matched. Height was similar for control subjects (1.80±0.08 meters) and patients (1.79±0.07 meters). Body weight (86±9 kg) and body surface area (2.05±0.13 m<sup>2</sup>) of patients were higher (*P*<0.05) than corresponding values of healthy subjects (72±12 kg, 1.90±0.18 m<sup>2</sup>). Informed consent was obtained from all subjects before the examinations, and the study was approved by our institutional committee on human research.

## MR Imaging

MR imaging studies were performed with the use of a standard Philips 1.5-T ACS-NT15 MR system (Philips Medical Systems International). The entire heart was imaged in the short-axis orientation with breath-hold multishot echo-planar imaging as described before.<sup>21</sup> MR imaging velocity mapping with retrospective ECG



**Figure 1.** Example of hemodynamic changes due to A-D stress in a 55-year-old male patient with hypertensive heart disease. Atropine sulfate was administered in 3 doses (A<sub>1</sub> to A<sub>3</sub>); the dobutamine infusion rate  $\gamma$  ( $\mu\text{g}/\text{kg}$  per minute) is indicated by the dark area. <sup>31</sup>P-MR spectra acquired at rest and during A-D stress from this patient are shown in Figure 2.

gating was performed to measure flow (expressed as mL/s) across the mitral valve and through the ascending aorta.<sup>13,22,23</sup> During the entire MR examination, SBP, DBP, and heart rate were recorded every 2 minutes with a Dinamap sphygmomanometer (Criticon). Image analysis<sup>24</sup> was performed twice on separate occasions by 1 observer with a minimal time interval of 7 days and by a second independent observer to determine intraobserver and interobserver variability.<sup>14</sup>

Functional parameters were calculated as described previously.<sup>14,22</sup> Peak rate of wall thickening and thinning were calculated as the maximal change in relative wall thickness/ms averaged for the LV circumference of a short-axis slice at two thirds of the LV long axis.<sup>25</sup> Acceleration and deceleration peak values were calculated as the maximal change in mL/s (expressed as mL/s<sup>2</sup>) obtained from the velocity encoded MR imaging acquisitions.

## <sup>31</sup>P-MR Spectroscopy and Statistical Analysis

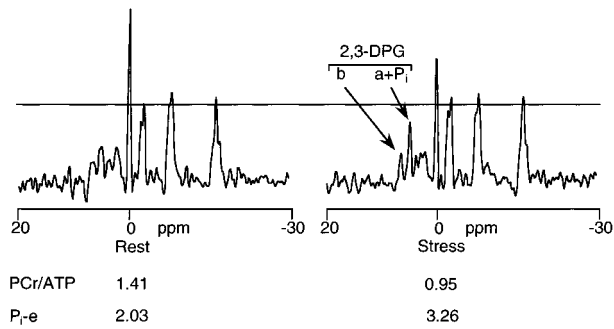
Once the MR imaging examination at rest was completed, subjects were studied with a Philips 1.5-T S15 MR system (Philips Medical Systems International). A 100-mm-diameter surface coil was used to acquire <sup>31</sup>P-MR spectra of the LV anterior wall with subjects in supine position. Volumes of interest were selected by image-guided spectroscopy with 3D-ISIS.<sup>26</sup> Other technical details were similar as described before.<sup>17,19</sup> After an acquisition at rest, control subjects and patients were subjected to an A-D stress test as described previously<sup>19</sup> (Figure 1). Blood pressures were recorded every 2 minutes with a Dinamap sphygmomanometer (Criticon) and were not allowed to exceed an SBP/DBP of 220/100 mm Hg in healthy control subjects and 250/130 mm Hg in patients, although these levels were never reached (Table 1 and Figure 1).

<sup>31</sup>P-MR spectra were quantified automatically in the time domain and were corrected for partial saturation effects and for the ATP contribution from blood with the use of methods described in previous studies.<sup>17,19</sup> As proposed in earlier work,<sup>19</sup> the ratio of the 2 resonance peaks in the spectral region of 2,3-diphosphoglycerate served as a semiquantitative estimate of myocardial inorganic phosphate (P<sub>i</sub>-e) signal intensity (Figure 2). Paired and unpaired 2-tailed *t* tests and linear regression analysis were applied when appropriate. A probability value of *P*<0.05 was considered to be significant.

## Results

### Myocardial Function

LV mass and LV mass index were statistically significantly higher in patients than in control subjects (Table 2). Systolic heart function was similar for patients and control subjects (Table 2) except for the peak rate of wall thickening, which



**Figure 2.**  $^{31}\text{P}$ -MR spectra obtained at rest and during A-D stress from anterior wall of LV of a patient with hypertensive heart disease. Hemodynamic changes due to A-D infusion in this particular patient are shown in Figure 1. Values of myocardial PCr/ATP and  $\text{P}_i$ -e are presented below the  $^{31}\text{P}$ -MR spectra. Myocardial PCr/ATP ratios were corrected for partial saturation effects and blood-ATP contamination, and line broadening of 15 Hz was applied. Inorganic phosphate (P) signal is obscured by overlapping signal from 2,3-diphosphoglycerate (2,3-DPG), which consists of 2 separate resonance peaks. When the 2,3-DPG<sub>a+P<sub>i</sub></sub> peak increases while the 2,3-DPG<sub>b</sub> peak is unchanged, the change in signal is most likely caused by an increase in  $\text{P}_i$ . Therefore a semiquantitative estimate of  $\text{P}_i$  signal intensity ( $\text{P}_i$ -e) was obtained by the ratio:  $(\text{DPG}_{a+P_i})/\text{DPG}_{b}$ , a dimensionless parameter. Limitations of  $\text{P}_i$ -e were discussed in a previous report.<sup>19</sup>

was significantly reduced in patients ( $P < 0.01$ ). LV filling in patients with hypertensive heart disease was impaired (Table 3). The peak rate of wall thinning, E/A ratio, early peak filling rate, and the early deceleration peak were lower in patients ( $P < 0.05$ ), whereas the atrial peak filling rate and atrial deceleration peak were higher ( $P < 0.05$ ) than those values in control subjects. No statistically significant correlations were found between the studied LV diastolic parameters and LV mass or LV mass index (all  $P > 0.05$ ). Functional measurements were highly reproducible, the intraobserver and interobserver variability being  $4 \pm 2\%$  and  $9 \pm 3\%$ , respectively.

## Myocardial Metabolism

Hemodynamic parameters at rest and during cardiac stress are presented in Table 1. An example of hemodynamic changes due to A-D stress in an individual patient is given in Figure 1. In patients at rest, SBP, DBP, and RPP were higher than in control subjects ( $P < 0.01$ ), but differences in SBP and RPP between patients and control subjects disappeared during stress. This means that control subjects and patients were stressed to an identical level of cardiac work load.

Figure 2 shows an example of  $^{31}\text{P}$ -MR spectra acquired from a patient at rest and during A-D stress. Table 1 and Figure 3 summarize the metabolic parameters obtained at rest and during stress. Myocardial PCr/ATP determined in patients was significantly lower both at rest ( $1.20 \pm 0.18$ ) and during stress ( $0.95 \pm 0.25$ ) compared with values obtained from healthy subjects at rest ( $1.39 \pm 0.17$ ,  $P < 0.05$ ) and during stress ( $1.16 \pm 0.18$ ,  $P < 0.05$ ). The observed decrease in myocardial PCr/ATP from rest to stress in patients and control subjects was statistically significant ( $P < 0.01$ ), whereas the percentile reduction did not differ between patients ( $-21 \pm 18\%$ ) and control subjects ( $-16 \pm 12\%$ ).

The semiquantitative estimate of myocardial  $\text{P}_i$  ( $\text{P}_i$ -e) determined in patients was higher both at rest ( $1.76 \pm 0.45$ ) and during stress ( $2.41 \pm 0.72$ ) compared with values obtained from healthy subjects at rest ( $1.43 \pm 0.26$ ,  $P < 0.05$ ) and during stress ( $1.92 \pm 0.39$ ,  $P > 0.05$ ) (Table 1, Figure 3B). The observed increase in myocardial  $\text{P}_i$ -e from rest to stress in patients and control subjects was statistically significant ( $P < 0.01$ ), whereas the percentile increase did not differ significantly between patients ( $47 \pm 46\%$ ) and control subjects ( $35 \pm 23\%$ ,  $P > 0.05$ ).

Values of myocardial PCr/ATP and  $\text{P}_i$ -e determined at rest in patients were similar to values obtained in healthy subjects during A-D infusion (Table 1, Figure 3). When rest and stress data obtained from healthy subjects and patients were pooled,

**TABLE 2. Left Ventricular Dimensions and Systolic Function**

Parameter	Control Subjects	Patients	Correlation ( <i>r</i> ) to PCr/ATP at Rest
LV mass, g	139±29	202±66*	-0.13
LV mass index, g/m <sup>2</sup>	73±13	98±28*	-0.06
End-diastolic volume, mL	164±30	161±33	0.18
End-systolic volume, mL	64±14	57±18	0.37
Stroke volume, mL	99±26	104±22	-0.02
Stroke index, mL/m <sup>2</sup>	52±13	51±10	0.12
Cardiac output, L/min	6.4±1.9	7.2±1.8	-0.29
Cardiac index, L · min <sup>-1</sup> · m <sup>-2</sup>	3.3±0.9	3.5±0.8	-0.20
Ejection fraction, %	60±9	65±7	-0.32
End-systolic wall stress, kN/m <sup>2</sup>	41±7	41±8	0.03
PRWTck, % mean thickness/ms	0.45±0.07	0.36±0.06*	0.28
AO peak ejection rate, mL/s	474±100	489±65	0.14
AO acceleration peak, mL/s <sup>2</sup> × 10 <sup>-3</sup>	8.31±2.48	8.75±1.38	0.04
AO deceleration peak, mL/s <sup>2</sup> × 10 <sup>-3</sup>	-3.87±0.76	-4.17±0.80	0.05

PRWTck indicates peak rate of wall thickening; AO, aortic.

LV mass, stroke volume, and cardiac output were also indexed to body surface area. Control vs patient or statistical significance of correlation; \* $P < 0.01$ .

TABLE 3. Left Ventricular Diastolic Function

Parameter	Control Subjects	Patients	Correlation (r) to PCr/ATP at Rest
PRWThn, % mean thickness/ms	-0.49±0.10	-0.37±0.05†	-0.55†
E/A peak flow	1.44±0.32	0.92±0.28†	0.40
E peak filling rate, mL/s	472±114	366±103*	0.45*
E peak filling rate/EDV, s <sup>-1</sup>	2.92±0.64	2.28±0.47*	0.36
E acceleration peak, mL/s <sup>2</sup> ×10 <sup>-3</sup>	8.99±2.55	7.32±3.17	0.42*
E deceleration peak, mL/s <sup>2</sup> ×10 <sup>-3</sup>	-4.29±1.44	-2.88±0.98*	-0.56†
A peak filling rate, mL/s	335±78	410±81*	-0.10
A peak filling rate/EDV, s <sup>-1</sup>	2.09±0.52	2.59±0.50*	-0.25
A acceleration peak, mL/s <sup>2</sup> ×10 <sup>-3</sup>	7.07±2.21	8.07±1.80	-0.15
A deceleration peak, mL/s <sup>2</sup> ×10 <sup>-3</sup>	-5.70±1.47	-7.20±1.76*	0.28

PRWThn indicates peak rate of wall thinning; E, early; A, atrial; and EDV, end-diastolic volume. Control vs patient or statistical significance of correlation: \* $P<0.05$ , † $P<0.01$ .

a highly significant correlation was found between the level of cardiac work load (RPP) and the myocardial PCr/ATP ratio ( $r=-0.53$ ,  $P<0.001$ ) and between RPP and myocardial  $P_{i-e}$  ( $r=0.51$ ,  $P<0.001$ ).

### Relation Between Function and Metabolism

Myocardial PCr/ATP acquired at rest was correlated with LV diastolic function indexes determined at rest (Table 3): peak rate of wall thinning ( $r=-0.55$ ,  $P<0.01$ ,  $y=-0.284x-0.066$ ), early peak filling rate ( $r=0.45$ ,  $P<0.05$ ,  $y=271.529x+70.403$ ), early acceleration peak ( $r=0.42$ ,  $P<0.05$ ,  $y=6.155x+0.224$ ), and early deceleration peak ( $r=-0.56$ ,  $P<0.01$ ,  $y=-3.963x+1.507$ ). However, myocar-

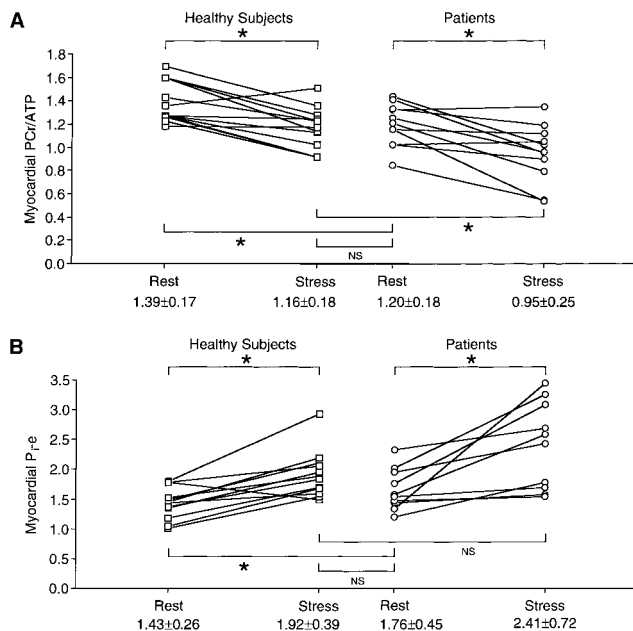
dial PCr/ATP was independent of measures of LV systolic function (Table 2). Myocardial PCr/ATP at rest was also correlated with SBP ( $r=-0.48$ ,  $P<0.05$ ) and DBP ( $r=-0.44$ ,  $P<0.05$ ) but not with LV mass index, age, and body weight. In addition, LV mass index correlated with SBP ( $r=0.71$ ,  $P<0.01$ ), DBP ( $r=0.64$ ,  $P<0.01$ ), and body weight ( $r=0.53$ ,  $P<0.01$ ).

## Discussion

### Myocardial Function

The present results are in close agreement with previous studies showing diastolic dysfunction in conjunction with normal LV systolic performance in hypertensive patients.<sup>2-4,7,8</sup> In accordance with previous studies<sup>2-4,6,7</sup> that used techniques other than MRI, our study shows that well-known diastolic parameters such as the E/A ratio and peak filling rate of early LV filling and new indexes of diastolic function such as the early deceleration peak were abnormal in hypertensive heart disease. Impairment of early diastolic LV filling was compensated by an increase in atrial LV filling, allowing normal systolic function. The only observed difference in systolic function between control subjects and patients was the maximum rate of wall thickening, which was reduced in patients and represents a very sensitive parameter<sup>25</sup> to detect contractility abnormalities. This may indicate that there is a gradual change from normal to impaired systolic function and that the presently studied patients were in the initial stage of this process.

Impairment of LV filling and the increased LV mass index suggest phenotypic alterations at the myocyte level of the hypertensive heart<sup>27</sup> different from physiological hypertrophy as can be seen in elite athletes.<sup>23,28</sup> In contrast to an increased cardiac load during part of the day as in athletes, hypertension causes a continuous pressure overload of the vascular system. Permanent cardiovascular overload causes myocyte stretch and increased angiotensin II concentrations in vascular and myocardial tissue<sup>29</sup> that is believed to trigger "genetic reprogramming."<sup>27</sup> This process promotes cell growth and extracellular matrix production, leading to an increase in myocardial mass and increased LV stiffness.



**Figure 3.** Changes in myocardial PCr/ATP (A) and myocardial  $P_{i-e}$  (B) due to severe A-D-induced stress in healthy subjects and patients with hypertensive heart disease. Note the transient decrease in myocardial PCr/ATP and increase in  $P_{i-e}$  from rest to stress in healthy subjects, rest in patients, stress in healthy subjects to stress in patients. Average values for myocardial PCr/ATP and  $P_{i-e}$  at rest and during stress are given below the Figure (mean ± SD). \* $P<0.05$ ; NS ( $P>0.05$ ).

### Myocardial Metabolism

The present results obtained at rest are in close agreement with previous human and animal studies. It has been reported that the myocardial PCr/ATP ratio determined at rest is subnormal when LV mass is increased.<sup>11,12,16,18,30–32</sup> Previous animal studies<sup>9,10,12,33</sup> that were specifically focused on heart disease due to pressure overload showed essentially the same results as presently found in humans. Even in the absence of evident LVH, overloaded hearts showed abnormalities in myocardial HEP metabolism.<sup>33</sup> We are not aware of any human studies that reported measurements of myocardial HEP metabolism in relation to hypertensive heart disease.

The presently observed decrease in myocardial PCr/ATP in the hypertensive heart at rest might be explained, at least partly, by the previously reported<sup>34</sup> decrease in creatine kinase activity and lower total creatine content in the hypertrophied human heart as determined from biopsy samples. Observations by Ingwall et al<sup>34</sup> suggest that pressure overload hypertrophy and ischemic heart disease bring about alterations in the creatine kinase system through a common stimulus. The presently observed changes in myocardial PCr/ATP and myocardial  $P_i$ -e in hypertensive hearts at rest may represent an adaptation toward demand ischemia similar to the normal human heart during severe pharmacological stress (Table 1 and Figure 3).

### Cardiac Stress Testing

The presently observed cardiac stress-induced decrease in myocardial PCr/ATP was similar for normal hearts and hypertensive hearts with increased LV mass, confirming results obtained in animal studies.<sup>31,35</sup> The correlations between RPP and myocardial PCr/ATP and between RPP and myocardial  $P_i$ -e suggest that myocardial HEP metabolism is a flexible system capable to adapt to a severe increase in cardiac work load. Even if the energy reserve equilibrium is already at a lower level at rest, as it is in hearts of patients with hypertensive heart disease, it further declines with increasing stress. The decrease in myocardial PCr/ATP observed during stress in healthy subjects, at rest in patients, and an even more severe decrease during stress in patients (Figure 3A) suggests a close relation between the myocardial PCr/ATP ratio and the level of cardiac work load. This knowledge could be of clinical value when patients are examined at rest only, as the value of myocardial PCr/ATP provides information on the severity of stress imposed on the hypertensive heart to maintain global heart function at rest.

This gradual adaptation to increasing cardiac work load might also explain why the myocardial PCr/ATP ratio determined at rest in patients with ischemic heart disease is close to values obtained from control subjects and why this ratio decreases during increased cardiac work only.<sup>15</sup> In mild ischemic heart disease there is no increased cardiac work load at rest because heart rate and blood pressures are normal, therefore global LV function is not affected. Only during cardiac stress the ischemic region poses a significant overload on the myocardium, which leads to an increased energy demand possibly related with global LV dysfunction.

The degree of stress imposed with high-dose A-D was substantial in the present study. Presently observed changes

in myocardial HEP metabolism due to stress testing are not to be expected at more moderate levels of stress. In a previous report<sup>19</sup> we showed that acquisitions in normal volunteers after a 15-minute recovery period yielded a PCr/ATP similar to its resting value, whereas the RPP was still 1.3 times its resting value. This was in agreement with the report by Weiss et al,<sup>15</sup> who did not observe any change in myocardial PCr/ATP in the normal heart at that same stress level.

### Relation Between Function and Metabolism

Several indicators of LV filling determined at rest show an association with myocardial HEP metabolism at rest. These results agree very well with the hypothesis previously postulated by Osbakken et al<sup>10</sup> that changes in myocardial creatine kinase kinetics may contribute to diastolic dysfunction. The biochemical mechanisms explaining the relation between myocardial HEP metabolism and diastolic heart function have not yet been elucidated. Ingwall et al<sup>34</sup> calculated that the phosphocreatine content in tissue with LVH is 4 times lower than in normal myocardium. We hypothesize that the lower phosphocreatine content, and a switch in substrate preference from fatty acids to glucose,<sup>12</sup> leads to lower levels of ATP at the sarcomeres in hypertensive hearts, which is not compensated for by increased mitochondrial ATP production. Lower cytosolic ATP levels lead to impaired  $Ca^{2+}$  sequestration by the sarcoplasmic reticulum and impaired relaxation in cardiomyocytes and may be responsible for diastolic dysfunction in hypertensive myocardium at the cellular level.<sup>5,36,37</sup>

Moreover, a recent study by Spindler et al,<sup>32</sup> with the use of a mouse model of familial hypertrophic cardiomyopathy, showed striking similarities with the present study. They concluded that changes in HEP content suggest that an energy-requiring process may contribute to the observed diastolic dysfunction, which is possibly related to a diastolic  $Ca^{2+}$  overload.

In previous studies in patients with hypertensive heart disease, correlations between the degree of hypertrophy and abnormalities of ventricular filling have been inconsistent.<sup>7,37</sup> In the present study, no relation was found between LV mass (or LV mass index) and LV function parameters and between LV mass and myocardial HEP metabolism. A previous report showed that LVH can occur independent of cardiac overload. It was demonstrated that angiotensin II-induced LVH in rats was independent of pressure overload, but that the occurrence of genetic reprogramming was dependent on pressure overload.<sup>38</sup> In another study it was shown that specific polymorphisms of the *ACE* gene may cause LVH in the absence of cardiac pressure or volume overload.<sup>39</sup> In addition, it was shown in the athlete heart that LVH alone is not associated with changes in LV function or myocardial HEP metabolism.<sup>23,28</sup> Moreover, abnormal LV filling has been demonstrated in hypertensive patients without LVH.<sup>2,4–8</sup> Therefore, it is not likely that LV mass is directly related to changes in myocardial function and myocardial HEP metabolism. LVH should be regarded as an epiphenomenon to cardiac overload and not as a primary factor causing abnormal LV filling.

### Limitations and Future Considerations

Underlying CAD could not be excluded with complete certainty, although none of the patients had evidence of CAD based on clinical history, clinical examination, ECG, or wall motion analysis by MR imaging. Moreover, hypertensive heart disease appears to be associated with a myocardial phenotype other than ischemic heart disease because in the former abnormalities in metabolism are present at rest, whereas in the latter exercise is needed to induce changes in the myocardial PCr/ATP ratio.<sup>15</sup>

Patients were gradually withdrawn from  $\beta$ -blockers 2 weeks before the MR examinations. The remaining ACE inhibitors and calcium antagonists were previously shown<sup>40</sup> to have no effect on exercise capacity. Therefore it is not likely that the present results can be explained by effects of antihypertensive medication.

In the present study, a limited number of subjects were studied, mainly because of the long examination time needed for the combined MR imaging and <sup>31</sup>P-MR spectroscopy examination and the severity of the A-D stress test. For the same and ethical reasons we had to choose between <sup>31</sup>P-MRS or MR imaging during A-D stress. However, the sample size was sufficient to show statistically significant differences between healthy control subjects and patients and significant correlations between myocardial function and metabolism determined at rest. Technical progress may soon allow MR imaging and <sup>31</sup>P-MR spectroscopy both at rest and during stress in the same comprehensive MR examination within a time period of 90 minutes.

In the present study we acquired the ratio of PCr over ATP as a measure of myocardial HEP metabolism. By using this ratio, a decrease in PCr due to an increase in cardiac work load may be underestimated because absolute amounts are not known. Furthermore, PCr/ATP ratios reported in the present study for the normal human heart at rest were in the lower range of previously reported values, which ranged from 0.9 to 2.1. In a previous report<sup>17</sup> we extensively discussed this issue and concluded that the major difference is most likely caused by the lower saturation correction factor used in the present study.

### Conclusions

Myocardial HEP metabolism is altered in patients with hypertensive heart disease. In addition, the present study is the first to provide evidence that there is an association between impaired LV diastolic function and altered myocardial HEP metabolism in humans. Furthermore, the subnormal myocardial PCr/ATP and supernormal myocardial P<sub>i</sub>-e in hypertensive hearts at rest may represent a condition similar to the normal human heart during severe cardiac stress. Therefore, the level of myocardial PCr/ATP and P<sub>i</sub>-e is most likely determined by the level of cardiac work load.

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