Journal of Cardiovascular Magnetic Resonance®, 2(2), 151–157 (2000)

INVITED PAPER

Magnetic Resonance Spectroscopy in Human Cardiomyopathies

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ABSTRACT

Magnetic resonance spectroscopy (MRS) can noninvasively provide a window into the metabolic status of the heart. This technique has shown abnormalities in the phosphocreatine-to-adenosine triphosphate ratio in patients with severe cardiomyopathies, either dilated or hypertrophic. Data indicate that abnormal metabolic parameters can risk stratify patients with dilated cardiomyopathy and provide independent prognostic information. Finally, the use of MRS in patients after cardiac transplantation is being explored. The information from cardiac MRS will likely provide the investigator and clinician with unique data and assist in the diagnosis and management of patients with various forms of heart disease.

KEY WORDS: *Cardiomyopathy; Hypertrophy; Phosphorus-31 spectroscopy; Transplantation.*

INTRODUCTION

Nuclear magnetic resonance spectroscopy (MRS) is a powerful noninvasive tool that can provide insight into the metabolic status of the myocardium. Over the past decade, investigators have examined animal models and patients with cardiomyopathies in an effort to understand the metabolic abnormalities associated with these pathophysiologic processes and define the role of MRS in humans. This review attempts to define where we are in this effort and to identify the role of MRS in diagnosing the severity and prognosis of cardiomyopathies.

Before addressing these issues, it is important to define the term "cardiomyopathy" and understand that the term may encompass several disorders that have distinct etiologies and manifestations. Perhaps the simplest definition is that which describes any global pathologic process that alters either the metabolism, anatomy, or function of the myocardium (1). Encompassed within this definition are disorders of decreased contractility without hypertrophy, usually due to a toxic exposure of drugs (e.g., alcohol or adriamycin), metabolic diseases (e.g., thyrotoxicosis), chronic volume overload (e.g., due to valvular heart disease), immunologic processes (e.g., after transplantation), and, perhaps most importantly, idiopathic processes. All these processes generally lead to a dilated cardiomyopathy (DCM) that is symptomatically manifested as congestive heart failure and is characterized by replacement of myocytes by fibroblasts and compensatory hypertrophy of the remaining myocytes (1). The diagnosis and accurate characterization of these processes in patients is crucial because of the prevalence of congestive heart failure in the population and its high morbidity and mortality.

Received March 14, 1999; Accepted December 28, 1999

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In contrast to DCM, hypertrophic cardiomyopathies (HCM) are generally a response to increased overload (e.g., aortic stenosis or hypertension), genetic abnormalities, or infiltrative diseases (e.g., hemochromatosis) and are characterized pathologically by increased wall thickness and replacement and hypertrophy of myocytes. Both DCM and HCM appear to share metabolic abnormalities, perhaps because of the late stage at which these processes have been diagnosed and investigated in humans.

ANIMAL STUDIES USING MRS

Models of both DCM and HCM have been studied using MRS to define the metabolic abnormalities in these conditions. The importance of these studies, despite their imperfect modeling of the complexity of human disease, is their ability to better define the metabolic abnormalities in cardiomyopathies and point us to the abnormalities observed in patients.

Numerous animal studies of cardiomyopathies have demonstrated reductions in the relative contents of the high energy phosphates phosphocreatine (PCr) and adenosine triphosphate (ATP), generally defined as the ratio of PCr/ATP. In general, the severity of the reduction in PCr/ATP has mirrored the severity of the pathologic insult. For example, McDonald et al. (2) examined remodeled myocardium in an open-chest canine model of left ventricular dysfunction produced by infarction of a distant myocardial region. Using an adiabatic pulse technique that provided localization to either the subendocardium or subepicardium, these investigators found a reduction of PCr/ATP in the subendocardium of hearts with left ventricular dysfunction when compared with normal hearts (1.71 ± 0.07 vs. 2.05 ± 0.7, $p < 0.05$) and evidence of phosphomonoesters not observed in the spectra of normal hearts. Although these phosphomonoester resonances may represent greater contamination of the myocardial spectra with the 2,3-diphosphoglycerate of blood, their presence has been associated with abnormalities in glycolytic metabolism and accumulation of glycolytic intermediates under ischemic conditions (3,4). Interestingly, these abnormalities were largely reversed with infusion of adenosine to increase blood flow, suggesting that the lower PCr/ATP ratio was a reflection of an oxygen supply–demand imbalance. Similar findings of reduced PCr/ATP were noted by Markiewicz et al. (5) in a Syrian hamster model of cardiomyopathy. In their study, verapamil also improved the metabolic abnormality, although the mechanism is unknown. These nuclear magnetic resonance studies validate the metabolic abnormalities previously observed using biopsy techniques (6).

The data in animal models of myocardial hypertrophy (left ventricular hypertrophy [LVH]) are less clear and, in general, only demonstrate metabolic abnormalities in models of severe hypertrophy or under conditions of severe imbalance of oxygen supply and demand. In a porcine model of modest LVH (34% increase in mass), Massie et al. (7) were not able to demonstrate any difference in PCr/ATP between control and LVH animals, either under baseline conditions or with increased oxygen demand. However, during dobutamine stimulation, glucose uptake and oxidation were greater in the LVH animals, consistent with a shift of metabolism from free fatty acids to glucose. In a similar study of animals with a 66% increase in left ventricular mass, Bache et al. (8) found a reduction in PCr/ATP and an increase in inorganic phosphate (P_i) in the subendocardium of LVH animals under pacing stress. These metabolic abnormalities were associated with significant reductions in the ratio of subendocardial and subepicardial blood flow, suggesting that the metabolic changes were due to ischemia. Interestingly, inotropic stimulation with dobutamine in these animals, although globally reducing PCr/ATP, did not result in a transmural gradient of these metabolites, a finding that was not altered by increasing blood flow with adenosine. These findings are more consistent with a regulatory response to inotropic stimulation, such as an increase in [ADP], than metabolic abnormalities indicative of ischemia.

Animal models also provide the opportunity to examine nuclei other than phosphorus and define abnormalities detectable by MRS that may be more specific or provide more understanding of the pathologic process than phosphorus-31 MRS. For example, using sodium-23 MRS, Jelicks and Siri (9) found that baseline levels of sodium were higher in compensated hypertrophied hearts than in either normal control or failing hearts. Coupled with the observation that intracellular sodium is higher in diabetic hearts (10), these studies indicate other potential nuclei that may provide additional information in human studies of cardiomyopathies.

HUMAN STUDIES USING MRS

Dilated Cardiomyopathy

Localization techniques allow the acquisition of spectra from the human heart with minimal contamination

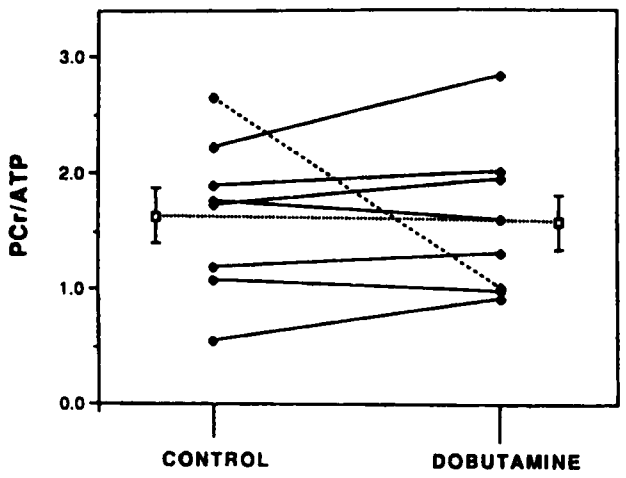

Figure 1. The metabolic response of myocardial high energy phosphates (PCr/ATP) in patients with DCM under conditions of inotropic stimulation with dobutamine infusion. Aside from one patient who was clinically unstable (dotted line), there was no reduction in PCr/ATP with dobutamine. (Adapted from reference 13.)

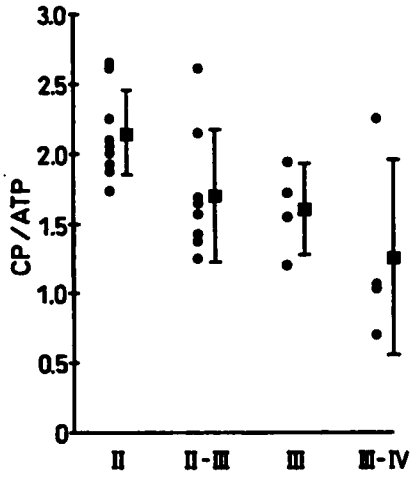

Figure 2. The relationship between PCr and ATP (CP/ATP ratio) as a function of NYHA grade I–IV. As the clinical status of the patients worsened and NYHA grade increased, PCr/ATP fell significantly. In addition, there was a highly significant relationship between NYHA grade and PCr/ATP ($r = 0.60$, $p < 0.005$). (Adapted from reference 15.)

from either skeletal muscle or blood (11). Initial studies of normal volunteers quickly expanded to studies of patients with cardiomyopathies. Schaefer et al. (12) examined 14 normal subjects and 17 patients to determine whether patients with either DCM (ejection fraction $\leq$ 30%) or LVH, either mild or severe, had metabolic abnormalities when compared with normal subjects. Briefly, this study found only a trend to lower PCr/ATP ratios in patients with DCM (0.70 $\pm$ 0.12 vs. 0.89 $\pm$ 0.08) but a marked increase in the phosphomonoester resonance similar to the findings of McDonald et al. (2) in their animal model.

This study was followed by an examination of eight patients with DCM using inotropic stimulation with dobutamine to test the hypothesis that increasing oxygen demand would worsen the metabolic state of these patients. Notably, dobutamine did not decrease the ratio of PCr/ATP in seven of eight patients (Fig. 1) (13). This finding suggested that myocardial ischemia did not play a role in the metabolic abnormalities of these patients and that [ADP] was not regulatory under these conditions. These findings corroborated those of the Syrian hamster model of cardiomyopathy (14) in which dobutamine did not alter high energy phosphate concentrations in animals with mild disease. Interestingly, the one patient who did have a significant reduction in PCr/ATP with stress was only marginally compensated, suggesting (as subsequently verified by others) that the clinical status of the patient with DCM is likely the most important predictor of metabolic abnormalities.

Definitive findings of lower PCr/AP ratios in patients with severe DCM were subsequently published by Neubauer et al. (15). Additionally, the PCr/ATP ratio correlated with the clinical severity of heart failure (as assessed by NHYA class) and furthermore improved with medical therapy in six patients (Fig. 2). This study was the first to indicate that phosphorus-31 spectroscopy could function as a clinical tool to assess the response to therapy.

Additional support for the role of MRS in patients with DCM was provided by these investigators in a subsequent study examining the predictive value of an abnormal PCr/ATP ratio in patients with DCM (16). Thirty-nine patients were followed for a mean of 2.5 yr after initial measurement of left ventricular ejection fraction, NYHA class, and PCr/ATP. Using a retrospective division of patients into normal (mean, 1.98 $\pm$ 0.07) and low (mean, 1.30 $\pm$ 0.05) PCr/ATP ratios, they found that both the PCr/ATP ratio and the NYHA class were independent predictors of both total and cardiovascular mortality (Fig. 3). In contrast to many studies of mortality in patients with congestive heart failure, ejection fraction did not provide additional prognostic information (16). Clearly, this study is enticing in that it suggests that MRS

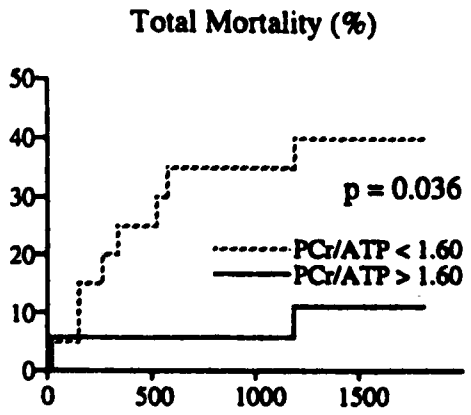

Figure 3. Kaplan-Meier life table analysis for total mortality in patients with DCM divided into groups with normal (>1.60) and low (<1.60) PCr/ATP. PCr/ATP was a better predictor of mortality than ejection fraction. (Adapted from reference 16.)

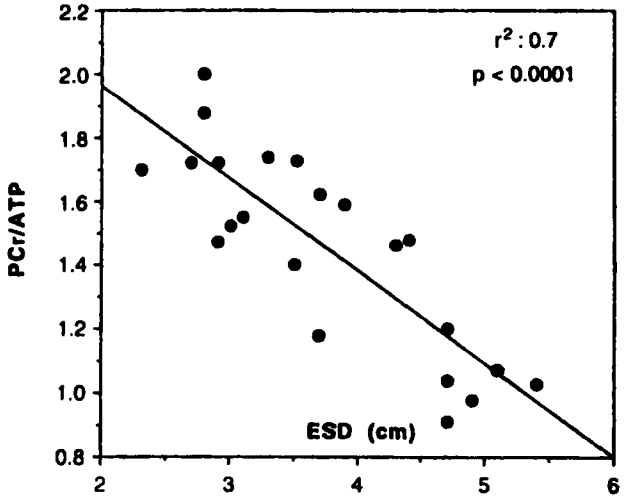

Figure 4. The relationship between PCr/ATP and end-systolic dimension (ESD) in patients with chronic mitral regurgitation. Similar relationships were found between these metabolic variables and left ventricular mass and shortening fraction, but not with wall stress. (Adapted from reference 18.)

has the potential to provide important prognostic information. However, the predictive role of MRS in relation to both clinical indicators and measures of left ventricular size and function must still be defined in a prospective trial.

Valvular Heart Disease

Valvular heart disease can cause either symptomatic or asymptomatic cardiomyopathy due to either pressure overload (such as in aortic stenosis) or volume overload (such as with aortic or mitral regurgitation). In either instance, increased wall stress in the common thread of these pathologic states, and it has been postulated that this increased wall stress, and hence oxygen demand, could result in metabolic abnormalities detectable by phosphorus-31 MRS. In addition, there has been the hope that identification of patients with abnormal metabolism could lead to appropriate and timely (but not unnecessary) valve replacement, thereby aiding in the surgical triage of these patients. Data demonstrate that abnormalities in PCr/ATP are present in patients with both aortic stenosis and mitral regurgitation. In the setting of pressure overload with aortic stenosis, metabolic abnormalities have only been observed inpatients with significant hemodynamic abnormalities (high wall stress) (17). In patients with volume overload due to mitral regurgitation, PCr/ATP was lower in those with severe regurgitation and evidence of hemodynamic sequelae such as left ventricular dilation (18) (Fig. 4). The value of phosphorus-31 MRS in deciding who should undergo valve replacement (independent of clinical and hemodynamic markers of disease severity) has not been tested in a large cohort of patients.

Hypertrophic Cardiomyopathy

Although there is clinical and pathologic overlap between patients with valvular heart disease or systemic hypertension leading to pressure overload and those with hypertrophy due to (congenital) myopathy, the latter patients have characteristics that predispose them to chronic myocardial ischemia and lethal arrhythmias. In addition, these patients have pathologic abnormalities that suggest a distinct process. Hence, investigators have sought to examine these patients to determine if the pathology is reflected in metabolic abnormalities. As in DCM, patients with even asymptomatic (but structurally severe) HCM have lower PCr/ATP ratios than control subjects (19,20). However, in contrast to DCM patients in whom the phosphomonoesters (PME)/ATP ratio is probably not altered by the disease process (20), these patients have elevated ratios (19) (Fig. 5). In addition, data show increased P_i and a lower pH in patients with HCM (20). In parallel to animal studies of hypertrophy, this finding has been interpreted to represent increased glycolytic flux and a shift away from oxidative metabolism.

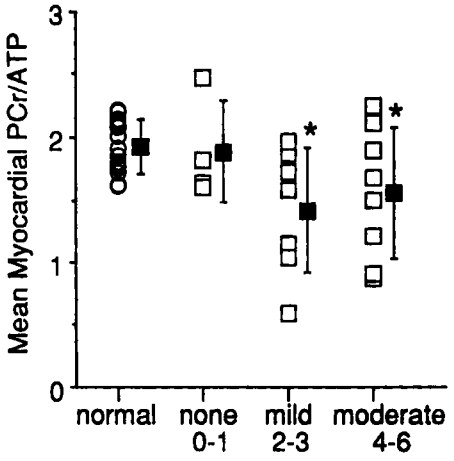

Figure 5. The ratio of PC4/ATP in normal subjects and in patients after cardiac transplantation. Although the ratio is significantly depressed in patients with either mild or moderate rejection, the overlap in the data make it difficult to separate these groups or to reliably differentiate individual abnormal measurements from the normal subjects. (Adapted from reference 22.)

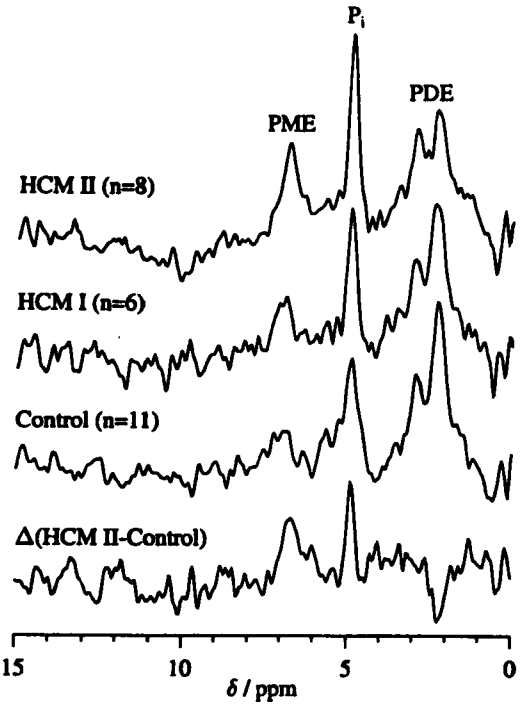

Figure 6. Average spectra from patients with severe HCM (HCM II), mild HCM (HCM I), and control patients demonstrating the increased PME and P_i resonances in patients with severe HCM. These spectra do not show the PCr or ATP resonances, which are further upfield. (Adapted from reference 19.)

Transplantation

Animal studies have shown that acute rejection results in dimunition of PCr/ATP that is proportional to the degree of rejection (21), likely due to the necrosis of myocytes due to this process. Unfortunately, the sensitivity and specificity of phosphorus-31 MRS in human hearts after transplantation, although separating rejecting from nonrejecting hearts, has not been sufficient to differentiate degrees of rejection (22) (Fig. 6). This may reflect the insensitivity of MRS to rejection or the relative inadequacy of localized endocardial biopsy to accurately diagnose a global rejection process. Recent data suggest that some transplant patients show a significant reduction in PCr/ATP with isometric exercise, consistent with microvascular abnormalities in oxygen delivery (23). This finding may allow MRS to provide information complementary to that of endomyocardial biopsy.

Adriamycin

Of the toxins capable of causing myocardial injury and therefore a global cardiomyopathic process, the antimetabolite adriamycin has been characterized most clearly. Adriamycin affects Na^+-Ca^+ exchange and calcium release via the ryanodine receptor and causes cytosolic calcium overload and hence cellular injury (24). Fluorine spectroscopy was used in conjunction with phosphorus spectroscopy to examine, in an animal model of acute adriamycin toxicity, whether the increases in Ca^{2+} were related to any metabolic abnormalities (25). This study did not demonstrate any changes in PCr, ATP, or P_i despite near doubling of intracellular Ca^{2+}. A clinical dilemma is titrating the total dose of adriamycin chemotherapy to provide adequate therapy without inducing cardiomyopathic injury. This is currently done by limiting the dose of adriamycin, which unfortunately results in toxicity in some patients that is only revealed late by left ventricular dysfunction. The hope that phosphorus-31 MRS would be able to monitor these patients during chemotherapy and optimize the dose based on evidence of cellular injury is as yet unrealized.

Peripheral Muscle Metabolism in Patients with Congestive Heart Failure

MRS has also provided important information on abnormalities of peripheral muscle metabolism in patients

with cardiomyopathies and clinical heart failure. These patients typically have reduced exercise tolerance due to abnormalities of peripheral muscle function. The characterization of these abnormalities and the relative roles of defects in cellular oxygenation, oxidative ATP synthesis, or metabolic efficiency have been targets of studies. Common findings from these studies of patients with DCM include a reduced phosphate potential and increased acidosis during exercise and slow recovery of PCr after exercise (26). Combining phosphorus and proton spectroscopy (to measure both phosphate compounds and deoxymyoglobin), Mancini et al. (27) determined that metabolic abnormalities in these patients (such as a greater increase in P_i/PCr with exercise) were not associated with greater deoxymyoglobin signals and were therefore not secondary to cellular hypoxia. This conclusion was supported by data obtained using near-infared spectroscopy showing comparable muscle oxygenation. The character of the metabolic abnormalities (given this equality of oxygenation) was elucidated by Kemp et al. (28) who found that the primary abnormality was decreased metabolic efficiency rather than a defect in mitochondrial oxidation.

CONCLUSION

Cardiac spectroscopy of patients with heart failure (either due to DCM or HCM) has been shown to detect abnormalities in high energy phosphates (PCr/ATP) in patients with cardiomyopathies. In general, metabolic abnormalities reflect either hemodynamic deterioration in patients with DCM or severe structural abnormalities in patients with HCM. The ability of spectroscopy to independently risk stratify patients with DCM is early evidence of the potential of MRS to provide important clinical information in patients with cardiomyopathies.

REFERENCES

1. Goodwin JF and Oakley CM. The cardiomyopathies. *Br Heart J*, 1972; 34:545–552.
2. McDonald KM, Yoshiyama M, Francis GS, Ugurbil K, Cohn JN and Zhang J. Myocardial bioenergetic abnormalities in a canine model of left ventricular dysfunction. *J Am Coll Cardiol*, 1994; 23:786–793.
3. Jeffrey FMH, Storey CJ and Malloy CR. Predicting functional recovery from ischemia in the rat myocardium. *Basic Res Cardiol*, 1992; 87:548–558.
4. Schaefer S, Carr LJ, Prussel E and Ramasamy R. Effects of glycogen depletion on ischemic injury in the isolated rat heart: insights into preconditioning. *Am J Physiol*, 1995; 268:H935–H944.
5. Markiewicz W, Wu SS, Parmley WW, Higgins CB, Sievers R, James TL, Wikman-Coffelt J and Jasmin G. Evaluation of the hereditary Syrian hamster cardiomyopathy by ^{31}P nuclear magnetic resonance spectroscopy: improvement after acute verapamil therapy. *Circ Res*, 1986; 59:597–604.
6. Jungling E and Kammermeier H. Rapid assay of adenine nucleotides or creatine compounds in extracts of cardiac tissue by paired-ion reverse-phase high-performance liquid chromatography. *Anal Biochem*, 1980; 102:358–361.
7. Massie BM, Schwartz GG, Garcia J, Wisneski JA, Weiner MW and Owens T. Myocardial metabolism during increased work states in the porcine left ventricle in vivo. *Circ Res*, 1994; 74:64–73.
8. Bache RJ, Zhang J, Path G, Merkle H, Hendrich K, From AHL and Ugurbil K. High-energy phosphate responses to tachycardia and inotropic stimulation in left ventricular hypertrophy. *Am J Physiol*, 194: 266:H1959–H1970.
9. Jelicks LA and Siri FM. Effects of hypertrophy and heart failure on [Na+)i in pressure-overloaded guinea pig heart. *Am J Hypertens*, 1995; 8:934–943.
10. Ramasamy R, Liu H, Oates PJ and Schaefer S. Attenuation of ischemia induced increases in sodium and calcium by the aldose reductose inhibitor zopolrestat. *Cardiovasc Res* 1999; 42:130–139.
11. Bottomley PA, Foster TH and Darrow RD. Depth resolved surface coil spectroscopy (DRESS) for in vivo ^{1}H, ^{31}P, and ^{13}C NMR. *J Magn Reson*, 1984; 59:338–342.
12. Schaefer S, Gober JR, Schwartz GG, Swieg DB, Weiner MW and Massie B. In vivo phosphorus-31 spectroscopic imaging in patients with global myocardial disease. *Am J Cardiol*, 1990; 65:1154–1161.
13. Schaefer S, Schwartz GG, Steinman S, Meyerhoff DJ, Massie BM and Weiner MW. Metabolic response of the human heart to inotropic stimulation: In vivo phosphorus-31 studies of normal and cardiomyopathic myocardium. *Magn Reson Med*, 1992; 25:260–272.
14. Buser PT, Camacho SA, Wu ST, Higgins CB, Jasmin G, Parmley WW and Sickman-Coffelt J. The effect of dobutamine on myocardial performance and high-energy phosphate metabolism at different stages of heart failure in cardiomyopathic hamsters: A ^{31}P MRS study. *Am Heart J*, 1989; 117:86–91.
15. Neubauer S, Krahe T, Schindler R, Horn M, Hillenbrand H, Entzeroth C, Mader H, Kromer EP, Riegger GAJ, Lackner K and Ertl G. ^{31}P magnetic resonance spectroscopy in dilated cardiomyopathy and coronary artery disease: Altered cardiac high-energy phosphate metabolism in heart failure. *Circulation*, 1992; 86:1810–1818.
16. Neubauer S, Horn M, Cramer M, Harre K, Newell JB, Peters W, Pabst T, Ertl G, Hahn D, Joanne SI, et al. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circulation*, 1997; 96:2190–2196.
17. Neubauer S, Horn M, Pabst T, Harre K, Stroemer H, Bertsch G, Standstede J, Ertl G, Hahn D and Kochsiek

K. Cardiac high energy phosphate metabolism in patients with aortic valve disease assessed by ^{31}P-magnetic resonance spectroscopy. *J Invest Med*, 1997; 45:453–462.

18. Conway MA, Bottomley PA, Ouwerkerk R, Radda GK and Rajogopalan B. Mitral regurgitation: impaired systolic function, eccentric hypertrophy, and increased severity are linked to lower phosphocreatine/ATP ratios in humans. *Circulation*, 1998; 97:1716–1723.
19. Jung WI, Sieverdring L, Breuer J, Hoess T, Widmaier S, Schmidt O, Bunse M, van Erckelens F, Apitz J, Lutz O and Dietze GJ. ^{31}P NMR spectroscopy detects metabolic abnormalities in asymptomatic patients with hypertrophic cardiomyopathy. *Circulation*, 1998; 97:2536–2542.
20. de Roos A, Doorbos J, Luyten PR, Oosterwaal LHMP, van der Wall EE and den Hollander JA. Cardiac metabolism in patients with dilated and hypertrophic cardiomyopathy: assessment with proton-decoupled P-31 MR spectroscopy. *J Magn Reson Imaging*, 1993; 2:711–719.
21. Canby RC, Evanochko WT, Barrett LV, Kirklin JK, McGiffin DC, Sakai TT, Brown ME, Foster RE, Reeves RC and Pohost GM. Monitoring the bioenergetics of cardiac allograft rejection using in vivo P-31 nuclear magnetic resonance spectroscopy. *J Am Coll Cardiol*, 1987; 9:1067–1074.
22. Bottomley PA, Weiss RG, Hardy CJ and Baumgartner WA. Myocardial high energy phosphate metabolism and allograft rejection in patients with heart transplants. *Radiology*, 1991; 181:67–75.
23. Evonochko WT, Buchthal S, den Hollander JA, Bourge R, Banza R and Pohost GM. Cardiac transplant patients assessed by the P-31 MRS stress-test [abstract]. *Soc Cardiovasc Magn Res*, 1998;1:94.
24. Pessah IN. Calcium release channel of sarcoplasmic reticulum: an important target for doxorubicin-mediated cardiotoxicity. *Adv Exp Med Biol*, 1992; 311:409–410.
25. Kusuoka H, Futaki S, Koretsune Y, Kitabatake A, Suga H, Kanada T and Inoue M. Alterations of intracellular calcium homeostasis and myocardial energetics in acute adriamycin-induced heart failure. *J Cardiovasc Pharmacol*, 1991; 18:437–444.
26. Massie B, Conway M, Yonge R, Frostick S, Sleight P, Ledingham J, Radda GK and Rajagopalan B. Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. *Circulation*, 1987; 76:1009–1019.
27. Mancini DM, Wilson JR, Bolinger L, Li H, Kendrick K, Chance B and Leigh JS. In vivo magnetic resonance spectroscopy measurement of deoxymyoglobin druing exercise in patients with heart failure: demonstration of abnormal muscle metabolism despite adequate oxygenation. *Circulation*, 1994; 90:500–508.
28. Kemp GL, Thompson CH, Stratton JR, Brunotte F, Conway M, Adamopoulos S, Arnolda L, Radda GK and Rajagopalan B. Abnormalities in exercising skeletal muscle in congestive heart failure can be explained in terms of decreased mitochondrial ATP synthesis, reduced metabolic efficiency, and increased glycogenolysis. *Heart*, 1996; 76:35–41.