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Creatine Kinase Kinetics Studied by Phosphorus-31 Nuclear Magnetic Resonance in a Canine Model of Chronic Hypertension-Induced Cardiac Hypertrophy

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To determine whether cardiac hypertrophy secondary to chronic renovascular hypertension is associated with altered in vivo myocardial metabolism, phosphorus-31 nuclear magnetic resonance saturation transfer techniques were used to study creatine kinase (CK) kinetics in six chronically hypertensive dogs with moderate cardiac hypertrophy and eight control dogs. The forward rate constant of CK and the flux of phosphocreatine to adenosine triphosphate were determined in both groups of dogs before and during norepinephrine administration (1 μg/kg per min), used to increase heart rate × systolic blood pressure (rate-pressure product), cardiac output and oxygen consumption.

Baseline and norepinephrine-induced changes in rate-pressure product, cardiac output and oxygen consumption were similar in both groups of dogs, as were baseline forward rate constant and flux of phosphocreatine to adenosine triphosphate. However, the norepinephrine-induced changes in forward rate constant and flux were significantly less in hypertensive than in control dogs ($p < 0.05$) even though changes in hemodynamic and functional variables were similar in both groups.

These data demonstrate that moderate myocardial hypertrophy is associated with altered CK kinetics, which do not appear to affect the heart's ability for global mechanical recruitment at this stage in the hypertensive process. It is possible that the changes in myocardial enzyme kinetics may contribute to diastolic dysfunction previously reported in this model and may be a precursor for ultimate development of heart failure if hypertension is maintained for prolonged periods.

The data also suggest that the heart of moderately hypertensive animals may work less per gram muscle and that it may have greater metabolic efficiency because it can maintain lower adenosine diphosphate levels (as indicated by lower forward rate constant of CK) than those of control hearts. However, it appears that either the CK system has a large safety factor such that the lower forward rate constant and flux found in hypertensive dogs is sufficient to support normal global mechanical function or that the phosphocreatine shuttle is not a critical factor in maintaining mechanical function in the moderately hypertrophied heart.

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Ventricular pressure overload can result from stenotic valvular disease, chronic hypertension and obstructive hypertrophic cardiomyopathy states. Although there is a reasonable understanding of the hemodynamic effects of pressure loading (1,2), there is a less clear understanding of the hypertension-induced changes in myocardial metabolism. It is accepted that these loading conditions stimulate the synthesis of contractile and structural protein with resultant increase in myocyte size and with ultimate necrosis and fibrosis (3). The factors that limit this process and those that are responsible for subsequent decreases in systolic and diastolic function are not well understood.

Because oxidative phosphorylation and the creatine kinase (CK) system are extremely important for organs with high energy demand, such as the heart, it is reasonable to hypothesize that abnormalities in these biochemical systems might lead to decompensation of mechanical function in hypertensive heart disease. There is some controversy concerning the status of these systems during the various stages of hypertrophy. Some investigators (4,5,7) report that myocardial high energy phosphate levels (phosphocreatine and adenosine triphosphate [ATP]) are decreased early in the hypertrophy process, increase back to normal levels during stable hypertrophy and are again decreased with progression to congestive heart failure; others (6,8–12) report no change during any stage of hypertrophy. In addition, some investigators (11,12) report that activity of enzymes such as creatine kinase (CK) and adenosine triphosphatase is depressed, possibly because of a change in isoenzyme distribution.

Previous studies from one of our laboratories (13,14) have

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demonstrated that moderate left ventricular hypertrophy secondary to chronic renovascular hypertension is associated with diastolic dysfunction, even when there are no systolic abnormalities or evidence of myocardial necrosis or fibrosis. The etiology of this pathophysiologic process is not well understood but may be related to abnormalities in oxidative metabolism. The present study was designed to explore the possibility that an abnormality in oxidative metabolism might contribute to recognized diastolic dysfunction. To this end, phosphorus-31 nuclear magnetic resonance (NMR) saturation transfer studies were performed in a canine model of renovascular hypertensive cardiac hypertrophy to determine the forward rate constant of CK (defined as the rate of formation of CK-phosphocreatine interaction divided by the quantity CK concentration multiplied by phosphocreatine concentration and presented in s^{-1}) and the flux of phosphocreatine to ATP (defined as velocity of the ATP synthesis by the CK system). The goal was to determine whether a metabolic abnormality might be a precursor of the mechanical dysfunction that ultimately occurs in hypertensive hearts.

Methods

Animal model. Chronic renovascular hypertension was produced in six dogs with a two-step procedure. All procedures were approved by the Animal Care Committee at the University of Pennsylvania and conformed to the "Position of the American Heart Association on Research Animal Use." Anesthesia was induced with Innovar-Vet, 2 ml intramuscularly and maintained with halothane, 1% to 2% as needed. In the first procedure, one kidney was exposed through a flank incision, wrapped in silk and then replaced into the retroperitoneum and the skin incision closed. The silk wrap induced fibrosis and subsequently a decrease in kidney size. In the second operation performed under similarly induced anesthesia approximately 2 weeks later, the opposite kidney was removed leaving the fibrotic silk-wrapped kidney in place. The remaining damaged kidney induced perinephric hypertension in all dogs (13), with blood pressure significantly increased from control levels (blood pressure 110/80 ± 10/10 mm Hg before kidney wrap and 160/110 ± 14/10 mm Hg after kidney wrap; $p < 0.05$). Dogs were followed up for 6 months with sequential echocardiography to document the change in heart size. When heart posterior wall thickness to end-diastolic dimension had increased approximately 50% from the prehypertensive condition, all dogs were studied in one final in vivo open chest experiment.

Animal preparation for nuclear magnetic resonance measurements. The 14 dogs (8 control, 6 with chronic hypertension) were sedated with Innovar-Vet (2 ml intramuscularly) and anesthetized with Nembutal (25 mg/kg body weight intravenously) (15). Tracheal intubation was performed for maintenance of the airway and for positive pressure ventilation. A cannula was placed in the femoral artery to monitor systemic blood pressure and arterial blood gases. A thermodilution catheter placed into the pulmonary artery by way of the right external jugular vein was used to measure cardiac output. A left lateral thoracotomy was performed to expose the heart and a pericardial cradle constructed to support the exposed heart. A double-tuned (hydrogen-1 = 116 MHz, phosphorus-31 = 46.9 MHz) NMR surface coil was placed on the left ventricle and maintained in place with cyanoacrylate.

Phosphorus-31 nuclear magnetic resonance saturation transfer measurements. After instrumentation, dogs were placed in a Plexiglas cradle and introduced into a 2.7-tesla, 30-cm bore superconducting magnet. After the resonant frequencies of gamma phosphate of ATP and phosphocreatine were determined from control spectra, saturation transfer experiments were performed with use of progressively increasing saturation times (0.1 to 5 s) for gamma phosphate of ATP while the change in phosphocreatine area was monitored (15). Pulse width was 70 μs and relaxation delay was 10 s. Cardiac and respiratory gating were used to trigger both saturation and acquisition radiofrequencies. Typical baseline saturation transfer data sets for control and hypertensive dogs are presented in Figure 1.

Changes in the areas of the phosphocreatine peaks were used to determine the forward rate constant of CK and the unidirectional flux from phosphocreatine to ATP with the following equation:

$$\frac{d M_{PCr}}{dt} = \frac{M_{oPCr} - M_{PCr}}{T_1} - K_f M_{PCr} \qquad [1]$$

whose solution is:

$$M_{PCr} = M_{oPCr}[1 - K_f \tau p(1 - e^{-t/\tau p})] \qquad [2]$$

where

$$\frac{1}{\tau p} = \frac{1}{T_1} + K_f \qquad [3]$$

and M_{PCr} = magnetization of phosphocreatine; M_{oPCr} = magnetization of phosphocreatine before saturation has been applied to gamma phosphate of adenosine triphosphate; T_1 = longitudinal relaxation; K_f = the forward rate constant of CK: τp = the time constant; and t = the saturation time (16,17). The magnetization is proportional to the area under the NMR spectral line for phosphocreatine. A least squares fit algorithm was performed by using equations [2] and [3] to solve for τp, K_f, and T_1. Flux = the product of M_{oPCr} and K_f.

Physiologic intervention. Saturation transfer experiments were performed in both groups of dogs during baseline conditions (without intervention) and during norepinephrine infusion (1 μg/kg per min) used to determine the heart's metabolic response to increased mechanical work loads. Heart rate × systolic blood pressure (rate-pressure product), cardiac output and oxygen consumption were monitored throughout all procedures as previously reported (15), and used to document hemodynamic stability throughout the saturation transfer measurements (Fig. 2 and 3).

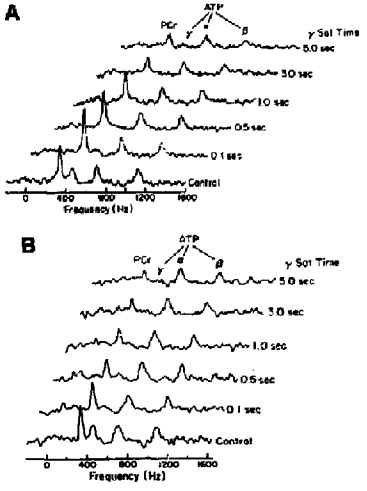

Figure 1. Examples of phosphorus-31 nuclear magnetic resonance saturation transfer data sets from a control dog heart (**A**) and the heart of a dog with chronic hypertension (**B**). The phosphocreatine (PCr) peak decreased as the gamma (γ)-adenosine triphosphate (ATP) peak was saturated for progressively longer times. α = alpha ATP; β = beta ATP; γ Sat Time = saturation time of γ ATP.

Cardiac ultrasound. Progressive changes in cardiac structure and function were studied with echocardiography (Diasonics, CV400) to document the hypertrophy process. Posterior wall thickness and end-diastolic dimension were determined from two-dimensionally guided M-mode echocardiograms of each dog. Change in the posterior wall thickness/end-diastolic dimension ratio was used to document myocardial hypertrophy (Fig. 4). All hypertensive dogs had at least a 50% increase in this ratio when the NMR saturation transfer study was done.

Gross morphology and histology. Autopsy studies for gross anatomic evaluation were performed in each dog. The heart was weighed and related to body weight obtained before death. The heart was sectioned (five standard sections involving the left and right ventricular free walls and septum) and stained with hematoxylin-eosin to evaluate histologic correlates of chronic pressure overload.

Statistics. Analysis of variance was used to provide statistical significance at the $p < 0.05$ level. Data are presented as mean values ± SD. To further exemplify the differences between the two groups, percent change from baseline data is presented for both groups.

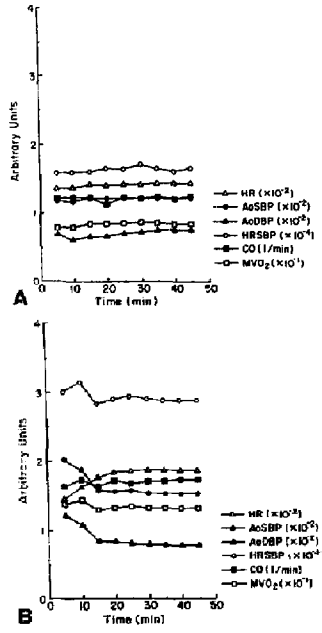

Figure 2. Mean hemodynamic variables during saturation transfer measurements in control dogs at baseline (**A**) and during norepinephrine-induced loading (**B**). Note that norepinephrine infusion was associated with an increase in rate-pressure product (HRSBP), cardiac output (CO) and oxygen consumption (MVO_2). All saturation transfer measurements were performed while the dogs were hemodynamically stable. During norepinephrine infusion, the rate-pressure product initially increased to high levels and later stabilized at increased but slightly lower levels. Saturation transfer measurements were begun at the point when rate-pressure product was judged empirically to be stable. Ranges of standard deviations for each point were rather large (up to ±50%) because of the variability from dog to dog, and are not included because they would confuse the point we are trying to make: saturation transfer measurements were made while each dog was hemodynamically stable. AoDBP and AoSBP = aortic diastolic and systolic blood pressure, respectively; HR = heart rate; l = liters.

Results

Anatomic changes. Heart weight/body weight ratio was 8.5 ± 0.3 g/kg for control dogs and 12.35 ± 1.3 g/kg for dogs with hypertension. The posterior wall thickness/end-

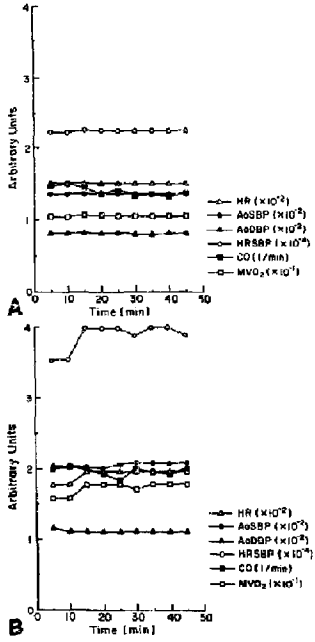

Figure 3. Hemodynamic variables of dogs with chronic hypertension during saturation transfer measurements: at baseline (A) and during norepinephrine-induced loading (B). Note that baseline rate-pressure product (HRSBP), cardiac output (CO) and oxygen consumption (MVO_2) are higher in hypertensive than in control dogs. In addition, norepinephrine infusion was associated with larger values for each of these variables; however, the percent changes from baseline were similar to those of the control group. All saturation transfer measurements were begun when dogs were judged empirically to be hemodynamically stable, generally after 15 min of infusion of norepinephrine. For the reasons noted in the legend to Figure 2, the ranges of standard deviations for each point were rather large (up to ±50%) and are not included in the figure. Abbreviations as in Figure 2.

diastolic dimension ratio increased from 0.21 ± 0.01 to 0.33 ± 0.04 ($p < 0.05$). At postmortem examination, all hypertensive dogs had moderate medial hypertrophy of the medium-sized coronary arterioles throughout the myocardium, consistent with the hypertensive process. Only one hypertensive dog had scattered myocardial fibrosis in the left

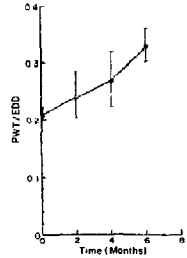

Figure 4. Mean change in echocardiographically determined posterior wall thickness/end diastolic diameter ratios (PWT/EDD) for hypertensive dogs during progression of chronic renovascular hypertension. These data are presented to document the presence of hypertrophy.

ventricle. Control dogs had no changes in the coronary arterioles or evidence of fibrosis.

NMR findings during norepinephrine infusion. Single phosphorus-31 NMR scans acquired at baseline and during norepinephrine infusion were similar in both control and hypertensive dogs. Nuclear magnetic resonance saturation transfer and average mechanical function data obtained during the saturation transfer measurements are presented in Table 1. At baseline, the absolute values of the forward rate constant of CK and flux of phosphocreatine to ATP were similar in the control and hypertensive dogs. During norepinephrine-induced increase in work loads, the forward rate constant and flux of phosphocreatine to ATP increased in control dogs but did not change significantly in hypertensive dogs even though there were similar increases in mechanical function in both groups.

Discussion

Metabolic effects of myocardial hypertrophy secondary to pressure loading. These effects have been evaluated in several animal models, including models of renovascular hypertension (8–10,18,19), aortic stenosis (20) pulmonary stenosis (21) and spontaneous hypertension (12). Myocardial hypertrophy is often associated with an increase in V3 isomyosin (8,9,20,21) and a decrease in mitochondrial CK (12). Other enzyme systems are also affected and include decreases in beta-hydroxy acyl coenzyme A dehydrogenase (18), citrate synthase (18,19), 3-oxoacid-coenzyme A transferase (19), acetoacetyl-coenzyme A synthase (19), and adenosine triphosphatase activities (9,11) and increases in hexokinase (18), lactate dehydrogenase (18,19), phosphorylase (19) and phosphofructokinase (19) activities. These enzyme changes are associated with increased rates of glucose use (19) and decreased rates of ketone body use (19). The decreased adeno-

Table 1. Cardiac Metabolic Changes in Control and Hypertensive Dogs

	Baseline		Norepinephrine		% Change (baseline to norepinephrine)	
	Control (n = 8)	Hypertensive (n = 6)	Control (n = 8)	Hypertensive (n = 6)	Control (n = 8)	Hypertensive (n = 6)
K_f	0.5 ± 0.2	0.4 ± 0.2	1.0 ± 0.5	0.5 ± 0.2*	92 ± 40	25 ± 40*
PCr	3.5 ± 0.7	3.7 ± 1.1	2.7 ± 0.9	2.8 ± 1.6	−21 ± 16	−24 ± 23
Flux	1.9 ± 0.9	1.6 ± 1.4	2.5 ± 1.3	1.3 ± 0.6*	32 ± 50	−18 ± 25*
HRSBP	1.8 ± 0.8	2.2 ± 0.5	3.1 ± 0.6	3.9 ± 0.9	73 ± 45	77 ± 27
CO	1.2 ± 0.8	1.4 ± 0.7	1.7 ± 1.2	2.0 ± 0.8	45 ± 40	43 ± 49
MVO_2	8.8 ± 3.2	10.2 ± 2.1	14.1 ± 2.4	17.2 ± 3.6	61 ± 30	69 ± 24

*$p < 0.05$, control versus hypertensive dogs. CO = cardiac output; Flux = phosphocreatine to adenosine triphosphate; HRSBP = heart rate × systolic blood pressure (rate-pressure product); K_f = forward rate constant of creatine kinase; MVO_2 = oxygen consumption; PCr = phosphocreatine.

sine triphosphatase activity was found to be associated with improvement of thermodynamic efficiency and required less oxygen for efficient oxidative phosphorylation (9). In addition, the rate of Ca^{2+} uptake and binding by the sarcoplasmic reticulum was decreased (10). Most of these previous studies evaluated enzyme activity in biopsy samples or heart extracts, or both, and therefore it is difficult to determine how these changes affected myocardial mechanical function.

The metabolic system in the hypertrophied heart: the creatine kinase shuttle. Since the heart is heavily dependent on oxidative phosphorylation to support its continuous mechanical function, we decided to evaluate this metabolic system in hypertrophied hearts. Oxidative phosphorylation produces the high energy phosphate, ATP, which is necessary for both contraction and relaxation of the myocardial muscle. When myocardial energy demand increases substantially (increased heart rate, blood pressure or intrinsic contractile function) or when oxidative mechanisms are markedly compromised (ischemia, hypoxia), either more ATP is required per unit time or it must be synthesized through other than oxidative mechanisms. To supply this extra or necessary energy for short periods of time, a separate enzyme system, the CK system, is used to rapidly convert phosphocreatine to ATP (and creatine). This system is called the CK shuttle. The forward rate constant of the CK reaction in reciprocal seconds (s^{-1}), defines the rate at which the enzyme system works. The flux of phosphocreatine to ATP is defined as the velocity of ATP synthesis.

Previous studies. Few studies have evaluated real time myocardial oxidative phosphorylation (bioenergetics) in an in vivo model of hypertensive hypertrophy (8–10,12). One of these studies (12) evaluated CK kinetics in an in vivo model of spontaneous hypertensive hypertrophy. In this model of rat spontaneous hypertension-induced myocardial hypertrophy, the baseline forward rate constant of CK and flux of phosphocreatine to ATP were found to be similar to control levels in 12- and 18-month old rats. In 12-month old hypertensive rats, as in control rats, CK kinetics responded to increased work load with an increased flux of phosphocreatine to ATP. However, 18-month old hypertensive rats did not have an appropriate increase in flux commensurate with increase in work load. These data suggest that in the older rats, the CK system may be critical for maintenance of mechanical work and that compromise of this system may be a premonitory event of heart failure. That study (12) was one of the first studies to evaluate the function of the phosphocreatine shuttle in maintenance or recruitment, or both, of the mechanical function of the heart.

Efficiency of the hypertrophied heart. In our model of canine renovascular hypertension, we found CK kinetics similar to those reported for the 18-month old spontaneous hypertensive rat model (12). In our model, the baseline forward rate constant of CK and the flux of phosphocreatine to ATP were similar to those found in control hearts; however, during similar norepinephrine-induced increases in mechanical work, the heart of hypertensive dogs did not significantly increase its forward rate constant of CK or flux of phosphocreatine to adenosine triphosphate, whereas these variables were increased significantly in the heart of control dogs. Because only one hypertensive dog had evidence of scattered myocardial fibrosis, and all hypertensive dogs had similar changes in CK kinetics (i.e., smaller change in the forward rate constant and flux of phosphocreatine to ATP) during norepinephrine infusion, it is unlikely that the changes were due merely to an anatomic lesion (i.e., loss of cardiomyocytes due to necrosis and ultimate fibrosis). These data suggest that the hypertensive heart works less per gram heart muscle (similar increases in rate-pressure product from baseline in a heart that weighs more, produced during lower synthesis of ATP through the CK shuttle) and that it works more efficiently than the control heart because it can maintain lower adenosine diphosphate levels (as indicated by the lower forward rate constant of CK) than can the control heart.

Clinical relevance. The present study was designed to determine whether there are metabolic changes that occur during progression of renovascular hypertension to myocardial hypertrophy. The main goal was to gain insight into possible mechanisms of pathophysiology that ultimately result in mechanical dysfunction in the hypertrophied heart. Baseline levels of phosphocreatine and ATP were similar in both control and hypertensive dogs, and these levels remained relatively constant during increased loading with

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norepinephrine infusion. However, recruitment of the CK system during norepinephrine loading was compromised in the hypertensive dogs even though global mechanical function was maintained within normal limits.

Previous studies in this laboratory (13,14) demonstrated that this model had diastolic dysfunction (characterized by a decreased early to atrial [E/A] inflow velocity determined by Doppler ultrasound, increased atrial filling fraction, decreased peak rates of wall thinning and filling determined by sonomicrometer, and prolonged time constant of isovolumetric relaxation). It is possible that the subtle metabolic changes found in the moderate myocardial hypertrophy of the present study are the basis for the aforementioned diastolic dysfunction; that is, the decrease in forward rate constant and flux (or velocity) of phosphocreatine to ATP might translate into the inability to increase ATP concentration by way of this system during increased demand. A subtle decrease in the rate of synthesis of ATP (which is necessary for both muscle contraction and relaxation) may delay myocardial relaxation during diastole and thus contribute to increased wall stiffness and compliance changes found in the earlier studies (13,14), even though global mechanical function is within normal limits. If these metabolic abnormalities progress, they may be a basis for heart failure.

Thus, an understanding of metabolic changes that occur during hypertensive processes in an animal model may provide insight into the pathogenesis of heart failure secondary to similar processes in a clinical patient population. These studies also point to the existence of metabolic abnormalities even in the early stages of hypertensive heart disease when there is no evidence of compromised hemodynamic or mechanical function. Early antihypertensive therapy may prevent progression of metabolic changes to ultimate mechanical heart failure.

Conclusions. The data obtained in the present study and from a previous study of Bittl et al. (12) can be interpreted as follows. It is possible that the CK system has a large safety factor, such that even the inability to increase the forward rate constant of CK and the flux of phosphocreatine to ATP during stress does not significantly affect global myocardial mechanical function until these values are decreased to <50% of baseline. In addition, these data suggest that changes in myocardial enzyme kinetics may contribute to diastolic dysfunction previously reported in this model of hypertensive hypertrophy, and may be a precursor for ultimate development of heart failure associated with chronic hypertension, even though the phosphocreatine shuttle may not be a critical factor in maintaining stability of mechanical function in the moderately hypertrophied heart during loading conditions that require recruitment of mechanical function.

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