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Research Article

The effects of phosphorus depletion on cardiac muscle function in six awake dogs were evaluated with surgically implanted transducers to serially measure ascending aortic root blood flow and high fidelity left ventricular pressure. After the animals recovered from surgery, phosphorus depletion was induced by feeding them a synthetic phosphorus-deficient diet plus aluminum carbonate gel for 35 days, followed by the same diet with phosphorus supplementation for 21 days. In addition to the cardiac studies, sequential measurements of phosphorus content in skeletal muscle and phosphorus in serum were obtained to ascertain the level of phosphorus depletion. Serum inorganic phosphorus concentration (mg/100 ml) decreased from 5.1 +/- 0.1 on day 0 to 0.9 +/- 0.1 on day 35 (P less than 0.01), and total muscle phosphorus (content mmol/100 g fat-free dry weight) decreased from 28.0 +/- on day 0 to 22.6 +/- 0.5 on day 35 (P less than 0.01). During the period of phosphorus depletion, there was no significant change in heart rate; however, stroke volume (milliliter) and peak blood flow velocity (centimeter per second) declined from 24 +/- 2 to 17 +/- 2 (P less than 0.01) and 121 +/- 12 to 98 +/- 7 (P less than 0.01), respectively. Maximum ascending aortic blood flow acceleration (centimeter per second square) and maximum left ventricular time rate of change of pressure [...]

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Reversible Depression in Myocardial Performance in Dogs with Experimental Phosphorus Deficiency

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ABSTRACT The effects of phosphorus depletion on cardiac muscle function in six awake dogs were evaluated with surgically implanted transducers to serially measure ascending aortic root blood flow and high fidelity left ventricular pressure. After the animals recovered from surgery, phosphorus depletion was induced by feeding them a synthetic phosphorus-deficient diet plus aluminum carbonate gel for 35 days, followed by the same diet with phosphorus supplementation for 21 days. In addition to the cardiac studies, sequential measurements of phosphorus content in skeletal muscle and phosphorus in serum were obtained to ascertain the level of phosphorus depletion.

Serum inorganic phosphorus concentration (mg/100 ml) decreased from 5.1 ± 0.1 on day 0 to 0.9 ± 0.1 on day 35 ($P < 0.01$), and total muscle phosphorus (content nmol/100 g fat-free dry weight) decreased from 28.0 ± 0.2 on day 0 to 22.6 ± 0.5 on day 35 ($P < 0.01$). During the period of phosphorus depletion, there was no significant change in heart rate; however, stroke volume (milliliter) and peak blood flow velocity (centimeter per second) declined from 24 ± 2 to 17 ± 2 ($P < 0.01$) and 121 ± 12 to 98 ± 7 ($P < 0.01$), respectively. Maximum ascending aortic blood flow acceleration (centimeter per second square) and maximum left ventricular time rate of change of pressure (mm Hg per second) also decreased from $4,630 \pm 313$ to $3,817 \pm 346$ ($P < 0.01$) and $2,582 \pm 347$ to $2,120 \pm 297$ ($P < 0.01$) during phosphorus depletion. After repletion all values returned to control values.

These results indicate that moderate diet-induced phosphorus depletion can depress myocardial perfor-

mance. With repletion of phosphorus, myocardial performance improves.

INTRODUCTION

Chronic phosphorus depletion has been associated with various functional and structural derangements in experimental animals and in man. These derangements include decreased hepatic oxygenation and abnormalities of liver function (1), cerebral dysfunction (2), erythrocyte rigidity and hemolysis (3), impaired phagocytosis by leukocytes (4), platelet dysfunction (5), and renal tubular defects (6).

Studies have shown that phosphorus depletion has an adverse effect on skeletal muscle function and composition (7-9). Specifically, a symptom complex characterized by muscle stiffness, weakness, and severe pain has been described in patients taking antacids containing aluminum hydroxide. These complaints were especially notable when serum phosphorus concentrations decreased to ≈ 1 mg/100 ml and improved rapidly with correction of the hypophosphatemia (7, 8). In addition, selective phosphorus depletion in experimental animals is characterized by a low resting transmembrane electrical potential difference, as well as changes in skeletal muscle composition consistent with a "sick" cell (9).

O'Connor and colleagues (10) have recently suggested that hypophosphatemia or phosphorus depletion or both may also have a deleterious effect on cardiac function. Their studies, however, were performed on critically ill patients who manifested, in addition to phosphorus depletion, a variety of toxic, metabolic, and nutritional derangements. As a result, the explicit role of phosphorus depletion in their findings cannot be ascertained.

We therefore investigated the effects of selective dietary-induced phosphorus depletion and repletion on cardiac muscle function in awake dogs by serially measuring high fidelity left ventricular pressure and

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aortic root blood flow. Peak velocity and maximum acceleration of blood ejected from the left ventricle (11) and the maximum rate of rise of left ventricular pressure ($\text{Max } dP/dT$) (12) were used to assess the contractile state of the myocardium.

METHODS

Six healthy adult, heartworm-free, male dogs, weighing 16–23 kg, were used in the study. A left thoracotomy was performed under aseptic conditions, using a general anesthetic (halothane). The ascending aorta was isolated and an appropriately sized electromagnetic flow probe installed (Biotronex Laboratory, Inc., Silver Spring, Md.) by the technique outlined by Khouri (13). A calibrated solid state, high fidelity pressure transducer (Konigsberg Instrument, Inc., Pasadena, Calif.) was inserted into the left ventricle at the apex, using the procedure described by Stone (14). The leads of the two transducers were externally placed at the back of the neck between the scapulae; the chest was closed and the animal allowed to recover.

With the dogs awake, ascending aortic blood flow and left ventricular pressure were recorded on magnetic tape (model 3960, Hewlett-Packard Co., Waltham, Mass.), beginning after a postsurgical recovery period of 14 days and then weekly for the duration of the study. During the recovery period, the animal was taken to the laboratory daily and trained to lie quietly for at least 30 min.

Phosphorus depletion was induced over a 35-day period after surgical recovery by feeding the animals 20 g/kg of a synthetic phosphorus-deficient, but otherwise nutritionally adequate, diet. Each 450 g contained 90 g protein, 270 g carbohydrate, and 45 g fat (ICN Nutritional Biochemicals Div., International Chemical and Nuclear Corp., Cleveland, Ohio). They were also given aluminum carbonate gel (Basaljel, extra strength, Wyeth laboratories, Philadelphia, Pa.), 60 cm^3/day . On chemical analysis, each 450 g of this diet contained 117 mg of elemental phosphorus and 160 meq of potassium. During the period of postsurgical recovery and during the 3-wk period of repletion, the same synthetic diet was used except that phosphorus was added as Na_2HPO_4 to provide a total elemental phosphorus intake of 1.87 g/day.

Measurement of blood flow velocity and acceleration. Aortic blood flow velocity was measured with a sine-wave electromagnetic flowmeter (model BL-613, Biotronex Laboratory, Inc.) and flow probes with various inside diameters (16–20 mm). For phasic flows, the flowmeter was operated at its highest nominal frequency setting (100), which gave a constant amplitude response within $\pm 5\%$ from 0 to 47 Hz and a linear-phase shift. Zero flow was taken as the flat portion of the curve during late diastole, and mean flow was obtained by electrical integration of the curve. Stroke volume was obtained by dividing mean aortic blood flow by heart frequency (beats per second).

The flow probes were calibrated *in vitro* using physiological saline and a section of aorta. Calibration factors for each probe were determined before implantation and at the end of the study after the dog had been sacrificed. The calibration factors remained essentially constant throughout the period of the study. The flowmeter was calibrated in units of velocity by dividing the flow calibration by the aortic cross-sectional area. This was calculated from the external aortic diameter (D) measured when the flow probe was implanted, and from the presumed thickness of the aortic wall (H), derived from the formula $H = 0.075D$ (15). Peak blood flow velocity was obtained from the maximum value of the measured volume flow curve using the velocity calibration.

Maximum blood flow acceleration (the maximum rate of change of blood flow velocity) was obtained in two ways. (a) The maximum slope of the initial upstroke of the blood flow velocity curve was measured directly from a fast polygraph (Electronics for Medicine, Inc., White Plains, N. Y.) tracing (100 mm/s) of the flowmeter signal. (b) A continuous record of acceleration was obtained by electrical differentiation of the phasic velocity signal. The differentiator (model BL-620, Biotronex Laboratory, Inc.) was operated at a nominal frequency setting (80), which gave a constant amplitude response within $\pm 5\%$, from 0 to 35 Hz. The differentiated velocity signal (acceleration) was then displayed along with the flow signal on a polygraph recording (Fig. 1). The differentiator was calibrated by correlating the peak differential with the graphically determined slope of the velocity signal at a fast paper speed (100 mm/s). At least six sequential flow complexes were used for the calibration.

Measurement of left ventricular pressure and its derivative. High fidelity left ventricular pressure was obtained from the implanted strain gauge transducer (Fig. 1). Resonant frequencies of these gauges are generally >1 kHz (16). This frequency response is well in excess of that required to obtain dynamic left ventricular pressure and its derivative (dP/dT) (17). The pressure transducers were precalibrated at 38°C , and the sensitivity did not change during the study. Because these transducers are likely to drift during implantation, absolute pressure levels were not recorded. The rate of change of left ventricular pressure (dP/dT) was obtained by electrical differentiation of the ventricular pressure signal. The dynamic frequency response of the differentiator was flat $\pm 5\%$, from 0 to 43 Hz. The continuous recording of dP/dT (Fig. 1) was calibrated in the same manner as the blood flow acceleration.

Procurement and analysis of samples of skeletal muscle. After the cardiac studies, we anesthetized the dogs with pentobarbital and, with the reported methods (9), sequentially

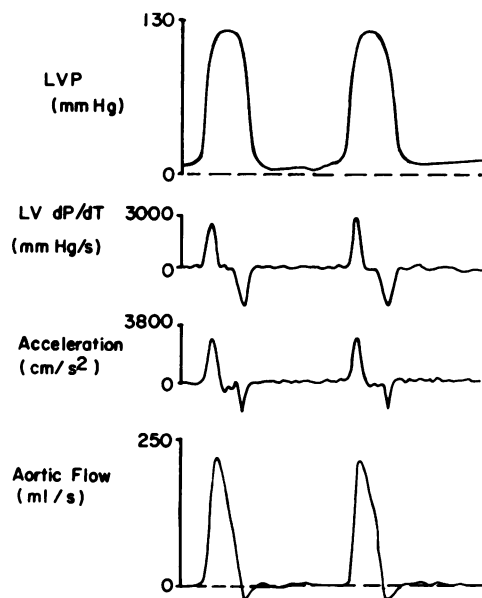


FIGURE 1 Control recordings obtained from a resting conscious dog. The simultaneous recordings of high fidelity left ventricular pressure (LVP), derivative of left ventricular pressure ($\text{LV } dP/dT$), derivative of ascending aortic blood flow velocity (acceleration), and ascending aortic blood flow are shown.

measured skeletal muscle content of phosphorus and serum inorganic phosphorus concentration. This was done to ascertain the level of peripheral phosphorus stores. Base-line phosphorus measurements were determined at the end of the postsurgical recovery period before phosphorus depletion was induced, repeated after 3 and 5 wk of phosphorus restriction, and again after 1 and 3 wk of phosphorus repletion. Blood samples were also collected at the same times to measure hematocrit, hemoglobin, creatine phosphokinase, electrolytes, pH, and PCO₂. Erythrocyte ATP concentration was also measured kit 35-UV (Sigma Chemical Co., St. Louis, Mo.) Body weight was monitored weekly. Body temperatures were obtained rectally at the time of skeletal muscle biopsies. No histologic studies were obtained.

Statistical analysis. Variables were measured on all six dogs on day 0 (control), after 3 and 5 wk of depletion (days 21 and 35), and after 1 and 3 wk of repletion (days 42 and 56). To know whether any of the variables changed significantly over the 56-day period, we used a two-way analysis of variance for each variable (18). The results in Table I list the significance level of the F test comparing the five time periods. Second, to compare the time periods to control for significant results ($P < 0.01$), we performed Dunnett's multiple range test (19). All data presented are means \pm SE.

RESULTS

Clinical effects of phosphate depletion. Initially, the dogs would consume all of their diet in a few minutes. During the last 2 wk of phosphorus depletion, however, four of the six dogs required gavage feeding to ensure complete intake of the diet. During the repletion period, their anorexia disappeared rapidly, and they again voluntarily consumed their

entire ration. In addition, after 5 wk of phosphorus depletion, five dogs showed some decrease in spontaneous activity but otherwise appeared normal. Weights did not significantly differ: day 0, 21.3 \pm 0.9; day 35, 22.0 \pm 0.7; and day 56, 22.1 \pm 0.7. Rectal temperatures taken at time of muscle biopsy also were not significantly different from control at the different time periods throughout the study.

Serum electrolytes, creatine phosphokinase, hematocrit, and blood gases. After 3 and 5 wk of phosphorus depletion, there was no significant difference in serum Na⁺, K⁺, Cl⁻, Mg⁺⁺, Ca⁺⁺, and creatine phosphokinase concentrations. Serum phosphorus, however, declined significantly, from an average control value of 5.1 \pm 0.1 to 1.0 \pm 0.1 mg/dl ($P < 0.01$) after 3 wk and to 0.9 \pm 0.1 mg/dl ($P < 0.01$) after 5 wk. A slight, but significant, decrease was also noted in hematocrit 46 \pm 2 to 41 \pm 2 ($P < 0.01$) and hemoglobin 15.5 \pm 1.0 to 13.6 \pm 1.0 g/dl ($P < 0.01$) after 5 wk. After phosphorus repletion the hematocrit and hemoglobin returned toward control values. There was no statistical difference after 3 and 5 wk in blood pH or PCO₂.

Erythrocyte ATP. 3 wk after phosphorus depletion erythrocyte ATP had decreased significantly, from a mean control value of 2.3 \pm 0.1 μ M/g to 1.3 \pm 0.2 μ M/g of hemoglobin ($P < 0.01$). After 5 wk, values were 0.8 \pm 0.2 μ M/g of hemoglobin ($P < 0.01$). With repletion, erythrocyte ATP values increased after 1 wk to 1.25 μ M/g ($P < 0.01$) and after 3 wk to 2.2 \pm 0.1 μ M/g, which was not statistically different from control values.

Skeletal muscle composition. After 3 wk of phosphorus depletion, total muscle phosphorus content had decreased \approx 13%, from 28.0 \pm 0.2 to 24.9 \pm 0.2 ($P < 0.01$), and by 5 wk \approx 19% to 22.6 \pm 0.5 ($P < 0.01$). With repletion, all values returned toward control values.

Cardiac function studies. Table II shows the effects of phosphorus depletion and repletion on cardiac function determinants. Although measurements were made weekly after recovery from surgery, only values during control (day 0), early (day 21), and late (day 35) phosphorus depletion and early (day 42) and late (day 56) phosphorus repletion periods are given. Weekly measurements, however, from one dog are shown in Fig. 2. Similar changes were observed in the remaining five dogs. During phosphorus depletion heart rate did not change significantly; however, average stroke volume and mean ascending aortic blood flow decreased 29% ($P < 0.01$) and 24% ($P < 0.01$), respectively. During phosphorus repletion both variables returned to their control values.

All three indices of myocardial contractility, maximum ascending aortic blood flow velocity and acceleration, and Max dP/dT showed evidence of myocardial depression during phosphorus depletion that was reversible during the period of repletion (Table II).

TABLE I

Results of Analysis of Variance for Testing Time Effect

Variable	Significance level
Serum	
sodium	0.06
potassium	0.28
chloride	0.13
calcium	0.06
magnesium	0.73
creatine phosphokinase	0.29
phosphorus	0.0001
Blood	
pH	0.71
PCO ₂	0.91
Erythrocyte	
ATP	0.0001
Skeletal muscle	
phosphorus content	0.0001
Cardiac function	
heart rate	0.33
stroke volume	0.0002
mean flow	0.0001
peak velocity	0.0001
maximum acceleration	0.0001
Max dP/dT	0.0001

TABLE II
Cardiac Function Studies

	Day		Heart rate	Stroke volume	Mean flow	Peak velocity	Maximum acceleration	Max dP/dT
			beats/min	ml	ml/s	cm/s	cm/s ²	mm Hg/s
Control	0	Mean	104	24	41	121	4,630	2,582
<i>n</i> = 6		±SE	±9	±2	±3	±12	±313	±347
Early PO ₄ deficiency	21	Mean	112	19	36	108	4,153	2,308
<i>n</i> = 6		±SE	±5	±2	±2	±10	±354	±277
		<i>P</i>	NS	<0.01	<0.01	<0.01	<0.01	<0.01
Late PO ₄ deficiency	35	Mean	115	17	31	98	3,817	2,120
<i>n</i> = 6		±SE	±9	±2	±3	±7	±346	±297
		<i>P</i>	NS	<0.01	<0.01	<0.01	<0.01	<0.01
Early PO ₄ repletion	42	Mean	116	21	39	111	4,179	2,505
<i>n</i> = 6		±SE	±8	±3	±4	±7	±326	±337
		<i>P</i>	NS	NS	NS	NS	<0.01	NS
Late PO ₄ repletion	56	Mean	117	22	42	123	4,446	2,616
<i>n</i> = 6		±SE	±6	±2	±3	±11	±329	±315
		<i>P</i>	NS	NS	NS	NS	NS	NS

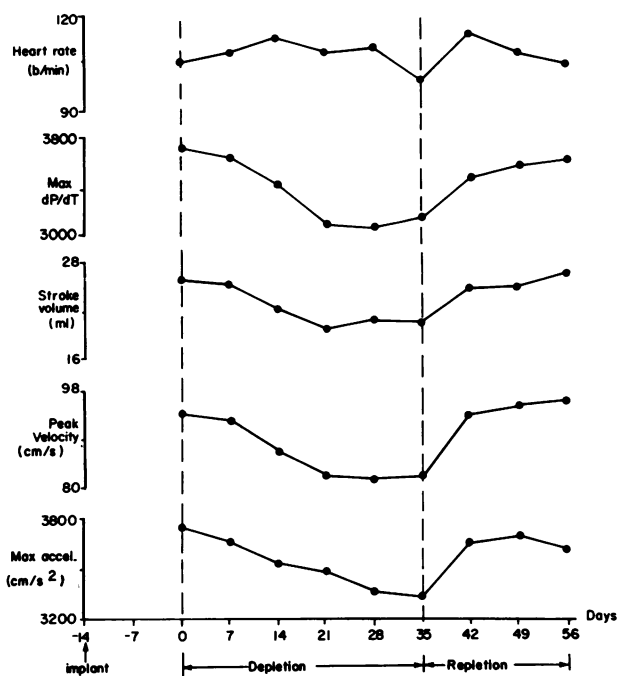


FIGURE 2 Effects in one dog of phosphorus depletion (35 days) and repletion (21 days) on heart rate, beats per minute (b/min), Max dP/dT , stroke volume, and maximum ascending aortic blood flow velocity and acceleration. 14 days were allowed for postsurgical recovery before beginning the study (day 0). Recordings were obtained weekly thereafter for the duration of the study.

Average Max dP/dT decreased a total of 18% ($P < 0.01$) during depletion, and average maximum velocity and acceleration declined 19% ($P < 0.01$) and 18% ($P < 0.01$), respectively. Measurements of maximum blood flow acceleration from all six individual dogs during control, early, and late phosphorus depletion periods and early and late repletion periods are shown in Fig. 3. In all six dogs this variable decreased

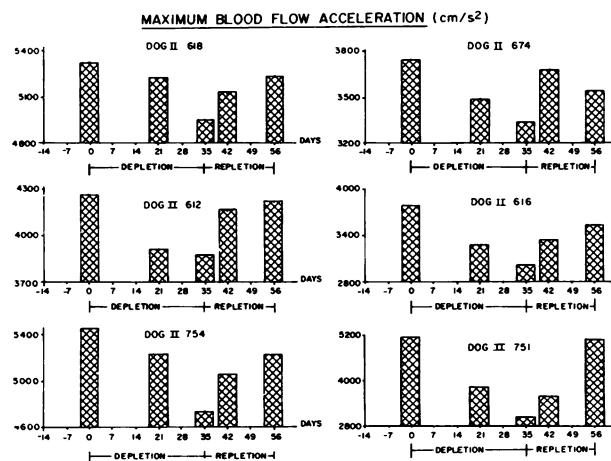


FIGURE 3 Histograms of maximum ascending aortic blood flow acceleration obtained from all six dogs during control (day 0), early (day 21), and late (day 35) phosphorus depletion and early (day 42) and late (day 56) phosphorus repletion periods.

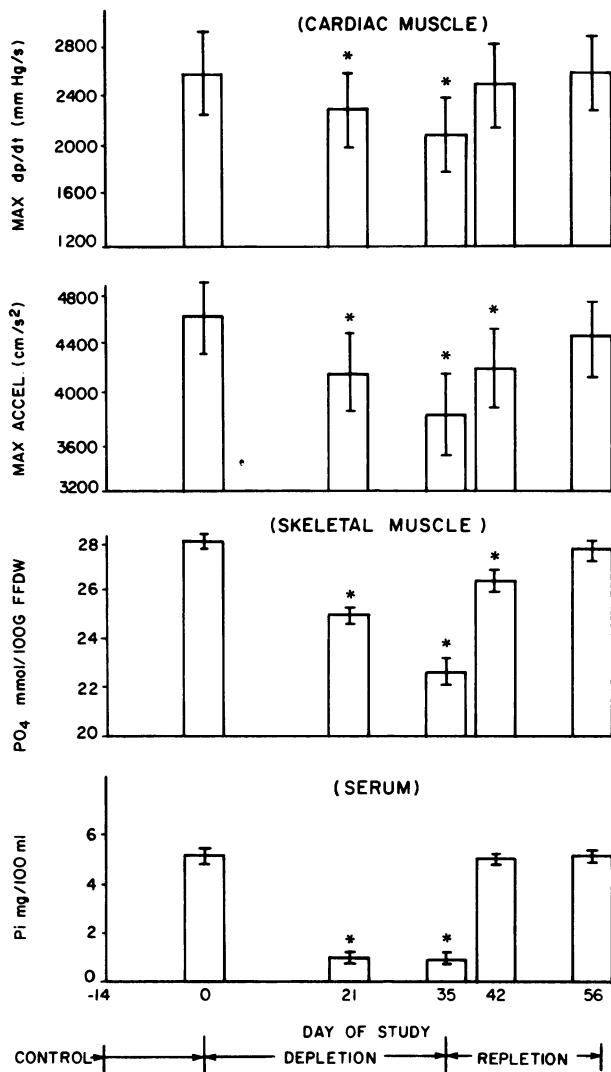


FIGURE 4 Relationship between Max dp/dt , maximum ascending aortic blood flow acceleration, skeletal muscle phosphorus content (PO_4), and serum inorganic phosphorus concentration (Pi) during control (day 0), phosphorus depletion (days 21 and 35), and phosphorus repletion (days 42 and 56) (*, $P < 0.01$).

during phosphorus depletion and returned to control values during repletion. Similar changes were also observed in maximum blood flow velocity and Max dp/dt in each animal.

Comparison of cardiac function determinants, serum phosphorus, and muscle phosphorus content. The relationship between Max dp/dt , maximum blood flow acceleration, muscle phosphorus content, and serum phosphorus concentration during control, phosphorus depletion, and repletion periods is illustrated in Fig. 4. As serum phosphorus and total muscle content

of phosphorus decreased, there was a concomitant drop in Max dp/dt and maximum acceleration, indicating a depression in myocardial contractility. During repletion, with the return of serum phosphorus concentration and muscle phosphorus content to normal, myocardial contractility also returned to control values as reflected by changes in Max dp/dt and maximum acceleration.

DISCUSSION

Mean ascending aortic blood flow and left ventricular stroke volume decreased in all animals during phosphorus depletion, whereas heart rate remained essentially unchanged ($P = NS$). In addition, maximum velocity and acceleration of aortic root blood flow and Max dp/dt decreased significantly during phosphorus depletion in all animals. These changes, in maximum acceleration and Max dp/dt , which are indicative of myocardial depression and independent of preload, afterload, and heart rate (11, 12, 20–24), paralleled the degree of phosphorus depletion (Fig. 4). This suggested that the observed changes in myocardial performance were a result of changes in phosphorus balance and not left ventricular volume, resistance to left ventricular ejection, or ventricular rate.

The use of velocity and acceleration of ascending aortic blood flow to assess left ventricular function was first suggested by Rushmer (25). Noble et al. (11) showed in conscious dogs that coronary artery occlusion caused a decrease in maximum acceleration, although cardiac output and arterial pressure remained essentially unchanged. Furthermore, they showed that changes of posture, with the presumed associated changes in end-diastolic dimensions or preload, did not alter maximum acceleration. Similar observations were made in conscious dogs by Kezdi et al. (20) during gradual coronary artery occlusion to induce myocardial infarction. Following this lead, other investigators (21) have used maximum acceleration to study the depressant effects of anesthetic agents on myocardial performance.

Considerable evidence also indicates that in conscious dogs maximum left ventricular dp/dt is a reliable index of the inotropic state of the myocardium (12, 22). These studies showed an increase in Max dp/dt with the administration of positive inotropic agents and a decrease with cardiac depressant drugs. This variable was only minimally influenced by changes in preload (volume infusion), afterload (phenylephrine administration), and heart rate (right atrial pacing). In a recent study of problems associated with the use of indices of myocardial contractility, Van Den Bos et al. (23) found in conscious dogs that both maximum blood flow acceleration and Max dp/dt

were less influenced than were other contractile indices, by changes in preload and afterload. In our studies, maximum blood flow velocity and acceleration decreased 19% ($P < 0.01$), and 18% ($P < 0.01$), respectively, with 5 wk of phosphorus depletion. During this same period Max dP/dT decreased 18% ($P < 0.01$) and average stroke volume decreased 29% ($P < 0.01$).

It appears evident, therefore, from these studies that phosphorus depletion depresses myocardial performance and is reversible with phosphorus repletion. Although we did not attempt to ascertain the mechanism of the decrease in myocardial performance with phosphorus depletion, a defect in the production or use of the high energy phosphate, ATP, known to be important to the process of contraction (26) is a likely candidate. This is especially true when one considers that depleted stores of ATP have been identified in all other cell sites studied in hypophosphatemic human subjects or animals (2–5, 27, 28).

Another possibility is that phosphorus depletion impairs Ca^{++} metabolism. Because Ca^{++} is essential at several points in the sequence of muscle activation and relaxation, phosphorus depletion could impair contractility by either producing a deficit in available intracellular Ca^{++} or alter its intracellular distribution or both (29). There was no significant difference in serum Ca^{++} ; however, a decrease in inorganic phosphate affects both the uptake of Ca^{++} by the cell as well as its intracellular distribution (30). In addition, in certain animal models, a decrease in cardiac contractility has been associated with an abnormality of Ca^{++} pumping by the sarcoplasmic reticulum (31). This function is dependent upon both ATP, which requires the availability of adequate stores of inorganic phosphate for resynthesis, and Ca^{++} -activated ATPase, which also could be affected by phosphate depletion.

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