2 THORNDIKE MEMORIAL LABORATORY 3

SECOND AND FOURTH MEDICAL SERVICES

1 HARVARD ~~MEDICAL UNIT~~ UNIV., BOSTON 2

BOSTON CITY HOSPITAL

26 Research Grant NsG-595 29

National Aeronautics and Space Administration

N67-34702 (ACCESSION NUMBER) 1 (THRU)
10 (PAGES) CR 65625 (NASA CR OR TMX OR AD NUMBER) 24 (CODE) 04 (CATEGORY)
FACILITY FORM 602

3 A Study of Physiological Mechanisms and Inter-Relations between Systemic and Regional Blood Volume, Blood Flow and Electrolyte Balance 4

6 Walter H. Abelmann, M.D.
Laurence E. Earley, M.D. 9

4/5 Interim Progress Report 6

9 June 30, 1967 10

(1) Renal Hemodynamics and Sodium Excretion

Studies on the interrelationship between renal hemodynamics and sodium and water balance in the dog have been continued. Since the last interim progress report (December 31, 1966) three additional phases of these studies have been completed.

a) Since previously reported studies carried out with the support of this grant have indicated that transmission of arterial pressure along the intrarenal circulation may be an important determinant of sodium reabsorption and excretion, the physiologic control of intrarenal vascular resistance could be a major factor involved in normal sodium balance. Therefore, the mechanism of autoregulation of renal blood flow and renal vascular resistance may have an important role in controlling sodium reabsorption and excretion and regulation of the extracellular fluid volume. Other investigators have suggested that autoregulation may be mediated via renin release and local (intrarenal) production and effect of angiotensin. To test this hypothesis we have studied autoregulation in the dog kidney during the renal arterial infusion of renin or angiotensin. Despite the vasoconstrictive effects of these agents renal vascular resistance still changed in response to induced changes in renal arterial pressure. In other words, constant infusions of vasoconstrictive amounts of renin or angiotensin did not prevent autoregulation of renal blood flow, suggesting that the phenomenon is not the result small changes in the endogenous intrarenal production and effect of angiotensin.

b) Earlier studies from this laboratory demonstrated that induced changes in renal vascular resistance, arterial pressure, and plasma oncotic pressure (protein concentration) result in changes in sodium reabsorption and excretion. However, such observations did not permit the conclusion that changes in these physical variables actually mediate the renal responses to changes in the extracellular fluid volume. Therefore, an additional series of studies was designed to control these physical variables during volume expansion. This was accomplished by various combinations of 1) induced renal vasodilatation, 2) infusion of hyperoncotic albumin during saline loading, 3) control of renal arterial pressure, and 4) volume expansion with plasma or whole blood rather than saline. The results indicate that changes in these physical variables (arterial pressure, renal vascular resistance, plasma oncotic pressure), either alone or in combination are major determinants of the effect of volume expansion to increase sodium excretion.

c) We postulated previously that physical factors mediate changes in sodium reabsorption and excretion via changes in the renal interstitial volume. Renal interstitial volume should increase (and sodium excretion increase) in response to increases in capillary hydrostatic pressure or decreases in plasma oncotic pressure (Starling forces). Therefore, we have measured directly the deep intrarenal hydrostatic pressure through wedged renal venous catheters, during maneuvers known to affect sodium excretion. Induced renal vasodilatation or infusion of plasma increase sodium excretion and result in striking increases in the intrarenal hydrostatic pressure. Infusion of saline may or may not increase the intrarenal

pressure, but when plasma protein concentration is restored during saline loading the maintenance of increased sodium excretion is associated with a rise in the intrarenal pressure. Therefore, increases in sodium excretion in the absenc of decreases in plasma protein concentration were always accompanied by increases in the intrarenal pressure. However, similar increases in sodium excretion produced by pharmacologic agents which block sodium reabsorption do not increase the intrarenal pressure. Intrarenal pressure was independent of arterial pressure, total renal blood flow, and urine flow. These observations support the suggestion that transmission of pressure into the kidney is a determinant of sodium reabsorption and excretion.

(2) The Effect of Atrial Fibrillation upon the Excretion of a Sodium Load

Investigations of the role of atrial size and function in the regulation of sodium excretion have been continued. Previous reports have described our studies of patients with mitral stenosis in atrial fibrillation and of patients with coronary or primary myocardial disease and atrial fibrillation, in whom excretion of the sodium load was generally delayed and incomplete, but was improved toward normal after cardioversion to normal sinus rhythm.

These studies have been extended to include measurements of systemic and renal hemodynamics. Preliminary evidence indicates that the sodium retaining effect of atrial fibrillation in intact man cannot be separated from the decrease in cardiac output and renal blood flow associated with this arrhythmia.

(3) Determinants of the Circulatory Response to Upright Tilt

Previous studies of the circulatory response to upright tilt in patients with heart disease had shown that such patients tolerate orthostatic stress remarkably well and tend to show an abnormal response, consisting of a smaller than normal increase in heart rate and diastolic pressure, often accompanied by less narrowing of the pulse pressure. This response was termed "heart failure response". It tended to be more frequent in the presence of clinical congestive heart failure, and correlated with the degree of abnormality of ventricular filling pressures, cardiac output, arterio-venous oxygen difference, and peripheral vascular resistance.

The role of ventricular filling pressures and circulating blood volume in determining this increased orthostatic tolerance was further tested by simulating these aspects of heart failure in the following manner. In five studies in 4 subjects 2 L of normal saline were infused over 1 - 2 hours, resulting in acute expansion of plasma volume and increase in central venous pressure. In all instances, heart rate and diastolic pressure increased less in response to upright tilt after expansion of plasma volume than in the control state.

Seven patients in congestive heart failure, tilted after 4 - 21 days of complete bedrest, maintained systolic blood pressure and increased diastolic pressure, at little increase in heart rate. Thus the increased tolerance of orthostatic stress protected patients with congestive heart failure from the orthostatic intolerance associated with "deconditioning" after prolonged bedrest.

In contrast, 13 patients convalescing from acute myocardial infarction, not in heart failure, showed a different response to 70° upright tilt after 9 - 24 days of bedrest. Asymptomatic, significant decreases in systolic pressure and pulse pressure were observed, while heart rate rose only little. Vaso-vagal reactions occurred in two patients in the 14th minute of tilt. Patients re-studied after full ambulation showed a normal response to upright tilt. These asymptomatic vasodepressor reactions are considered to represent a potential threat to the heart and brain, and have led to the suggestion that blood pressure be monitored closely when patients with recent myocardial infarction are mobilized.

Current studies are aimed at the elucidation of the pathogenesis of these abnormal postural vasodepressor responses, and may contribute to our understanding of the deconditioning process associated with immoblization.

These studies of the determinants of the circulatory response to upright tilt again emphasize the role of dehydration in orthostatic intolerance. They suggest that maintenance of adequate hydration and, when indicated, rehydration prior to mobilization after immobilization or space travel may, at least in part, prevent orthostatic intolerance.

Another implication for space medicine is that subjects who develop acute myocardial damage may be especially prone to develop orthostatic intolerance after immobilization and possibly also after exposure to zero gravity.

(4) Hemodynamic Effects of Phosphate Supplements in Paget's Disease of Bone

As part of a collaborative study of interrelations between metabolic and hemodynamic abnormalities in diseases associated with demineralization of

bone, 3 patients with extensive involvement of the skeleton by Paget's disease were studied before, during and - in two cases - after cessation of oral supplements of inorganic phosphate. Without supplementation, all 3 patients displayed abnormally high cardiac outputs (6.3 - 7.7 L/min), low total peripheral resistance (984 - 1188 dyne-sec-cm^{-5}), and low arterio-venous oxygen differences (3.7 - 4.4 vol. per cent). During supplementation, all 3 patients showed reduction in cardiac output (-20 to -26 per cent), increased total peripheral resistance (+22 to +46 per cent), decreased left ventricular work index (-12 to -40 per cent), and increased arterio-venous oxygen difference (+3 to +39 per cent). Within three months after being switched to placebo, all cardiovascular parameters had returned to near control levels. In addition, during supplementation, all patients displayed moderate to complete relief of pain, decreased urinary calcium excretion, and positive calcium balance, having shown greatly accelerated bone turnover rates in the control state.

These data suggest that oral phosphate supplements favorably affect the abnormal cardiovascular dynamics of Paget's disease and promote calcium retention in this disorder.

PUBLICATIONS IN 1967

1. Martino, J. A., and Earley, L. E.: Depressed tubular sodium absorption (T_{Na}) during water loading. Clinical Res. 15: 364, 1967 (Abstract).

2. Friedler, R. M., Belleau, L. J., Martino, J. A., and Earley, L. E.: Hemodynamically induced natriuresis in the presence of sodium retention resulting from constriction of the thoracic inferior vena cava. J. Lab. Clin. Med. 69: 565, 1967.

3. Martino, J. A., and Earley, L. E.: Demonstration that renal hemodynamics and plasma oncotic pressure are mediators of the natriuretic response to volume expansion. J. Clin. Invest. 46: 1092, 1967 (Abstract).

4. Martino, J. A., and Earley, L. E.: The effects of infusion of water on renal hemodynamics and the tubular reabsorption of sodium. J. Clin. Invest. (in press).

5. Martino, J. A., and Earley, L. E.: Demonstration of the role of physical factors as determinants of the natriuretic response to volume expansion. J. Clin. Invest.(in press).

6. Abelmann, W. H., and Fareeduddin, K.: The circulatory response to upright tilt in patients with heart disease. Aerospace Med. 38: 60 - 65, 1967.

7. Benson, H., Goldsmith, R. S., Ingbar, S. H., Abelmann, W. H., and Braverman, L. E.: Hemodynamic and metabolic effects of phosphate supplements in Paget's disease of bone. J. Clin. Invest. 46: 1035 - 1036, 1967 (Abstract).