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

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(1) Regulation of Sodium Excretion

Studies on the mechanisms for regulating sodium excretion have been continued in the dog, and recently these projects have been extended to the human subject. During the past six months two major areas have been explored and are described below.

a) Earlier studies supported by NsG 595, which have been reviewed in previous reports, have led to the suggestion that hemodynamic factors (viz., arterial perfusion pressure, plasma oncotic pressure, and renal vascular resistance) may alter the tubular reabsorption of sodium by intrarenal pathways. A recently completed study in the dog has provided evidence that these physical factors are important mediators of the natriuretic response to volume expansion, and thus, indicating an important physiologic role for non-hormonal, physical factors as determinants of sodium excretion.

b) Clearance and micropuncture studies have provided abundant data regarding the effects of various maneuvers (volume expansion, diuretic infusion, vena caval constriction, etc.) on proximal tubular reabsorption of sodium in the dog and rat. However, virtually no data has been available on the tubular anatomy of sodium reabsorption in the human, and to what extent sodium reabsorption by the human nephron resembles that of the dog and rat. We have utilized the technique of

diuretic induced "distal tubular blockade", previously described from our laboratory, to study sodium reabsorption in the human. The results demonstrate that proximal and distal tubular reabsorption of sodium in the human resembles qualitatively that in the rat and dog. In the human proximal tubular reabsorption of sodium is decreased during "escape" from a mineralocorticoid and is increased in the upright position and in patients with cirrhosis or congestive heart failure.

These general studies are being continued in an effort to identify further the role of non-hormonal hemodynamic and physical factors as determinants of normal and abnormal regulation of sodium excretion.

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

(a) Studies in Man

Investigations of the role of atrial size and function have been continued. As reported previously, in patients with mitral stenosis and atrial fibrillation excretion of a sodium load was generally delayed and incomplete, but was improved toward normal after cardioversion to normal sinus rhythm. Extension of these studies to patients in atrial fibrillation associated with arteriosclerotic heart disease disease, thyrotoxicosis, primary myocardial disease and to

patients without evidence of heart disease has revealed that generally, retention of a sodium load was less abnormal, and no changes were evident after conversion to regular sinus rhythm.

In selected patients, these studies included measurements of systemic and renal hemodynamics. Although this group is still small, the data suggest that cardioversion from atrial fibrillation to sinus rhythm results in an increase in cardiac output as well as renal plasma flow, while glomerular filtration rate remains unchanged.

(b) Studies in the Dog

A model animal has been developed, suitable to study interrelationships between atrial arrhythmia, atrial pressure, cardiac output, renal hemodynamics, and sodium excretion. Reversible atrial fibrillation as well as reversible mitral stenosis can be produced in this animal. Studies carried out in the open-chested animal have indicated the desirability of changing this model to a closed-chest one. This is in progress.

(3) Determinants of the Circulatory Response to Upright Tilt

Previous reports have summarized our studies of the tolerance of orthostatic stress, including the response of heart rate and blood pressure, in a broad sample of patients with cardiovascular

disease. The increased tolerance of passive upright tilt observed in patients with clinical as well as subclinical heart failure was attributed primarily to increased circulating blood volume and raised ventricular filling pressures. As predicted by this concept, the "heart failure response" could be produced in normal subjects by means of acute expansion of plasma volume. Also, patients in congestive heart failure were resistant to deconditioning by either acute plasma volume depletion or prolonged bedrest. In contrast, a vasodepressor response to upright posture, whether tilt or sitting, was found in some patients convalescing from acute myocardial infarction.

Most of these studies had been done in unbloody manner, in order to avoid affecting the phenomenon under study by instrumentation. The hypothesis that expansion of plasma volume, whether artifically in the healthy subject or by disease in the cardiac patient, is the prime determinant of tolerance of orthostatic stress is now being tested by studying the hemodynamic response to orthostatic stress in selected subjects and patients. Preliminary results, on the basis of 13 subjects, indeed suggest that a larger circulating blood volume, of whatever cause, permits better maintanence of cardiac output in response to orthostatic stress.

The previous recommendation that the role of dehydration in orthostatic intolerance be emphasized stands.

Publications

July 1 - December 31, 1967

1. Martino, J.A., and Earley, L.E.: The effects of infusion of water on renal hemodynamics and the tubular reabsorption of sodium.