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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) Renal Hemodynamics and Sodium Excretion

During the past grant period, laboratory investigations in the dog have been continued to extend previous observations of relationships between renal hemodynamics and sodium excretion. During the past year we reported studies demonstrating that the tubular reabsorption of sodium relates to the effectiveness with which renal perfusion pressure is transmitted along the intrarenal circulation. Renal vasodilatation alone decreases sodium reabsorption, and increased renal perfusion pressure, in the presence of reduced renal vascular resistance, also reduces sodium reabsorption. These observations indicate that renal vascular tone and perfusion pressure could play important roles in determining sodium balance, and therefore in regulating the extracellular fluid volume.

Utilizing a technique of diuretic (ethacrynic acid and chlorothiazide) induced blockade of distal tubular reabsorption, it has been possible to localize changes in sodium reabsorption to the proximal tubule. Thus the effect of perfusion pressure to alter sodium reabsorption occurs in the proximal tubule. We have also demonstrated that a direct relationship exists between plasma oncotic (protein) pressure and proximal tubular reabsorption. On the basis of these observations it was suggested that proximal tubular reabsorption may relate inversely to the renal interstitial volume, and that hydrostatic and oncotic pressures affect this mechanism in opposite directions via changes in capillary wall perfusion.

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These same lines of investigation are being continued to explore (1) The relationships between physiologic renal vascular autoregulation and the control of sodium balance, and (2) the extent to which these hemodynamically induced changes in tubular reabsorption and sodium balance determine the excretory response to volume expansion with (1) water, (2) saline, (3) plasma, and (4) blood.

(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 in the regulation of sodium excretion have been continued. Previous reports have described our studies of patients with mitral stenosis 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.

A series of patients with coronary or primary myocardial disease and atrial fibrillation, studied recently, have shown similar normalization of sodium after restitution of normal sinus rhythm, irrespective of heart rate. Indirect evidence suggests that the sodium retaining effect of atrial fibrillation, at least in part, is hemodynamically mediated, the arrhythmia interfering with the atrial transport function. Current studies are exploring the mediation of this effect further.

b) Experimental Studies in Dogs

Further studies of the mechanism by which atrial fibrillation alters sodium excretion are being carried out in the dog, under circumstances permitting the control of the variables involved. An electrical

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method was developed, permitting atrial fibrillation and defibrillation at will. Initial studies in the open-chested dog have given evidence of alteration of excretion of sodium and water with alteration in atrial rhythm, but the findings have not been consistent. Further studies are in progress.

(3) Determinants of the Circulatory Response to Upright Tilt

A previous report described the initial studies of the cardiovascular response of patients with heart disease to prolonged upright tilt. In general, cardiac patients displayed rather good orthostatic tolerance, accompanied by a smaller than normal increase in heart rate and diastolic blood pressure and by less narrowing of the pulse pressure. This response was termed "Heart Failure Response", although it did not correlate with degree of clinical heart failure.

Subsequently, in six subjects and in 34 patients with cardiovascular disease who had supine hemodynamic studies at a separate time but in a comparable state, the responses of heart rate and blood pressure were analyzed in relation to hemodynamic variables.

The response of heart rate to upright tilt correlated negatively and significantly with right atrial, left atrial, and pulmonary arterial pressure ($R = - 0.44$, $- 0.50$, and $- 0.41$ respectively); it correlated positively and significantly with cardiac index ($R = + 0.31$). The response of diastolic pressure to tilt correlated significantly with right atrial pressure ($R = - 0.31$) and with stroke index ($R = + 0.39$).

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There was no significant correlation with cardiac rhythm or digitalis status.

Prolonged bedrest is known to result in decreased orthostatic tolerance in normal subjects, resulting in abnormally large increases in heart rate and fall in blood pressure in response to upright tilt. Of nine patients with heart disease who were studied after prolonged bedrest and prior to mobilization, both patients in congestive heart failure retained the "heart failure response" and showed no evidence of deconditioning. Seven patients with myocardial infarcts and no evidence of heart failure showed an excessive tachycardia and fall in blood pressure, evidence of deconditioning. Normal orthostatic tolerance returned within a week after ambulation.

All of 5 normal subjects responded to acute volume depletion by intravenous ethacrynic acid with decreased orthostatic tolerance, while 3 of 4 patients in congestive heart failure tolerated the upright posture relatively well after double the volume of diuresis.

It is concluded that patients with heart failure tend to be able to maintain blood pressure in response to upright tilt at little or no increase in heart rate, reflecting increased orthostatic tolerance or "overconditioning". Patients with congestive heart failure may be resistant to deconditioning by bedrest or by volume depletion.

These studies serve to delineate the role of ventricular filling pressures and circulating blood volume as determinants of orthostatic tolerance.

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Studies of the effects of acute depletion of blood volume and of acute expansion of blood volume are in progress.

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