Diminished Forearm Arteriolar Dilator Capacity Produced by Mineralocorticoid-Induced Salt Retention in Man

Implications Concerning Congestive Heart Failure and Vascular Stiffness

By Robert Zelis, M.D., and Dean T. Mason, M.D.

SUMMARY

The mechanism of the increased stiffness of peripheral vessels in patients with congestive heart failure (CHF) is unknown. It was considered that an increased sodium (Na⁺) content of peripheral vessels, shown in experimental CHF, might lead to diminished arteriolar dilator capacity. Thus, Na⁺ retention was induced in six normal volunteers by the daily oral administration of 0.2 mg of fludrocortisone acetate (F) and 10 g NaCl for 1 week. This induced a weight increase of 3.1 lb and increased serum Na⁺ and decreased serum potassium concentrations (P < 0.02). The peak reactive hyperemia blood flow (RHBF) was measured plethysmographically in the forearm before and after treatment. Upon restoration of the circulation after 1, 5, and 10 min of ischemia the peak RHBF was 21.8, 33.1, and 34.9 ml/min/100 ml before administration of F and NaCl but was reduced to 19.6 (P > 0.2), 28.6 (P < 0.02), and 24.4 (P < 0.02) ml/min/100 ml by treatment. Thus, steroid-induced salt retention leads to diminished vascular compliance. Furthermore, it is suggested that increased vascular Na⁺ content is causally related to the vascular stiffness abnormality characteristic of CHF.

Additional Indexing Words:
Arterial sodium
Peripheral resistance
Vessels of forearm
Plethysmography
Fludrocortisone
Reactive hyperemia blood flow

IT NOW is acknowledged that certain characteristic alterations of the peripheral circulation attend the congestive heart failure state,¹⁻⁵ and that one of these abnormalities is an important modification of the peripheral vascular resistance to endogenous and exogenous dilator stimuli.¹ Thus, in the limbs, the blood flow responses to exercise, temporary ischemia, and vasodilator drugs are markedly attenuated in patients with heart failure. It has recently been suggested that the cause of this abnormality of arteriolar dilator capacity is an increased sodium content of the peripheral vessels.⁶ To test this hypothesis, it was decided to administer the mineralocorticoid, fludrocortisone,* to a group of normal subjects to determine the effects of salt and water retention on the circulatory dynamics and reactive hyperemia response of a specific vascular bed, that of the forearm.⁷

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¹ Florinef - E. R. Squibb & Sons, New York, N. Y.
Methods

After informed consent was obtained, six normal volunteers (age 27.3 ± 1.2 SEM years) without evidence of heart disease, peripheral vascular disease, or hypertension were studied on two occasions 7 days apart. Forearm blood flow was measured by the venous occlusion technic with a collecting pressure of 30 mm Hg using a single strand mercury-in-rubber strain gauge plethysmograph placed at mid-forearm. The wrist cuff was inflated to suprasystolic pressures for at least 1 min prior to the recording of blood flow. Resting blood flow was taken as the average of six to 10 recordings 15 sec apart after the subjects had reached a basal state for 15 min in a 71°C room. The reactive hyperemic response was determined in the forearm after release of 1, 5, and 10 min of arterial occlusion. Following restoration of the circulation to the ischemic limb, blood flow determinations were made at 5 sec, 15 sec, and every 15 sec thereafter until blood flow had returned to base line values. The reactive hyperemia response to 5 min of occlusion was determined in duplicate. Oral fludrocortisone acetate, 1 mg, was administered initially and then 0.2 mg of the drug along with 10 g of sodium chloride was given daily for 1 week. At the end of this time, the reactive hyperemia response was redetermined under comparable conditions. Blood pressure and weight were recorded daily, and serum electrolytes were determined before and at the end of the 1 week of treatment. In nine additional subjects who were untreated, the peak reactive hyperemia response was determined on two separate occasions 1 week apart.

Results

The six subjects who received fludrocortisone acetate increased their weight by 3.05 ± 0.76 lb (P < 0.01), increased their serum sodium concentration 4.5 ± 1.3 mEq/L (P < 0.01), and decreased their serum potassium concentration 0.45 ± 0.15 mEq/L (P < 0.02). There was no significant change in blood pressure or the circumference of the forearm under the gauge. Resting forearm blood flow decreased from 5.70 ± 1.35 to 4.12 ± 0.95 ml/min/100 ml (P < 0.05). The peak reactive hyperemia blood flow (RHBF) in the forearm following release of 1 min of arterial occlusion was unchanged by treatment with the mineralocorticoid and salt. However, following release of 5 and 10 min of arterial occlusion, the peak RHBF was significantly reduced (P < 0.02) (fig. 1). To increase the validity of the measurements of the peak reactive hyperemia response, the duplicate 5-min determinations and the 10-min determination of the peak RHBF were averaged since it has been previously demonstrated that these values are not significantly different. In the six subjects who received fludrocortisone, the peak RHBF decreased from 34.1 ± 2.43 to 28.2 ± 3.56 ml/min/100 ml (P < 0.01). In contrast, in the nine subjects of similar age who were untreated, the peak RHBF did not change over a comparable interval (36.1 ± 2.21 to 39.3 ± 2.13 ml/min/100 ml [P > 0.2]).

Discussion

Fludrocortisone acetate is a potent mineralocorticoid which has been shown to increase total body sodium and produce fluid retention even in normal subjects. This was evidenced in the present study by the weight gain and significant increase in the serum sodium concentration of the six subjects who received the drug. The increase in total body sodium produced by mineralocorticoid administration

![Figure 1](image_url)

The peak reactive hyperemia blood flow ± SEM of six subjects as a function of the duration of arterial occlusion, before (control, solid line) and during treatment with fludrocortisone acetate (fludrocortisone, broken line).
has been shown to be widely distributed: An increased sodium content has been described in skeletal muscle and kidney. Therefore, although not directly demonstrated in the present study, it is reasonable to assume that the vascular sodium content also was increased in the six subjects receiving this drug. Indeed, sodium concentration is increased in the peripheral arteries in dogs with experimentally produced congestive heart failure.

In the six subjects who were to receive the mineralocorticoid, the initial determination of the peak reactive hyperemia blood flow was normal. This was expected since the subjects had no evidence of vascular disease, hypertension, or heart failure. However, following 1 week of treatment with fludrocortisone and a high salt intake, there was a significant attenuation of the peak reactive hyperemia blood flow response in the forearm after release of 5 and 10 min of arterial occlusion. The peak RHBF following withdrawal of a maximal ischemic stimulus (5 or 10 min of ischemia) has been shown to be a good indicator of the distensibility of the peripheral arterial bed. Thus, immediately upon release of arterial occlusion, the normal resistance vessels are widely dilated, and the principal determinant of the blood flow to an extremity in terms of resistance to flow becomes that offered by the large arteries and capillary bed. Therefore, the determination of reactive hyperemia blood flow has received wide usage as a circulatory function test in patients in the detection and assessment of atherosclerotic peripheral vascular disease.

In addition to atherosclerosis of the peripheral arteries, disease of the resistance vessels themselves also can cause a decrease in the peak reactive hyperemic blood flow. Thus, a significant attenuation of the peak RHBF has been shown with systemic hypertension and with systemic amyloidosis. Likewise, in congestive heart failure, there is diminished distensibility of the peripheral arterioles. Since in both heart failure and hypertension vascular sodium content is increased, it has been postulated that perhaps the cause of the vascular stiffness shown in the extremities in these two conditions is due to the increased sodium content of the vessels. The finding of a diminished peak RHBF in the present study caused by mineralocorticoid-induced salt retention extends these previous observations and strongly suggests that the vascular stiffness abnormality characteristic of congestive heart failure is, at least in part, the result of increased sodium content in the systemic arterioles. Alternatively, it is also possible that the mineralocorticoid may have increased tissue pressure which by increasing resistance to flow through the capillary bed may have influenced the peak reactive hyperemic response.

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ROBERT ZELIS and DEAN T. MASON

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