REGULATION OF INTRAVASCULAR VOLUME IN CHRONIC CONGESTIVE FAILURE*

BY

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One of the most remarkable evidences of biological defence is the preservation of intravascular volume and pressure. This is often done against difficult odds, and therefore with varying degrees of success.

The key defect in chronic congestive heart failure is the inability of the muscle fibres to shorten sufficiently to deliver an adequate stroke volume. This is all the more amazing when it is appreciated that the dilated heart is (according to the laws of physics) better equipped to deliver volume (less shortening of each fibre is required) than to develop tension (as represented by heart size and systemic pressure) (Levine *et al.*, 1960). In any event the end-result is a cardiac output deficient in relation to bodily needs.

Various organs respond in different ways to this situation. Some regions, like the skin and muscle, simply receive less blood per unit time and register their deficit through altered physical function, as fever secondary to low skin blood flow and undue exertional fatigue secondary to inadequate muscle flow. Others, like the kidney and sensitive areas of the neurovascular system, react in such a way as to conserve or expand bodily fluid—a form of non-specific negative feedback. This is seen in any low output or low volume state, as, for example, in most forms of shock. Finally, the liver may contribute in part simply through inadequate deactivation of certain hormones naturally predisposing to sodium and fluid retention. Let us concern ourselves with two responses: (1) decrease in vascular capacitance; and (2) increase in vascular volume. (a) Role of kidney, and (b) role of aldosterone and of anti-diuretic hormone.

The most natural response is a decrease in the flow of blood through non-essential areas. In fact, we have been astounded to find that even the coronary system participates in the general vasoconstriction of congestive heart failure (Messer *et al.*, 1960). In recent years numerous workers have demonstrated that the veins undergo a constriction such that their capacity is decreased at any given pressure—blood consequently is driven centripetally toward the heart. Wood *et al.* (1955) have shown that this venoconstrictor response can be prevented by autonomic blockade, and has its afferent receptor in the ischaemic tissue.

At the same time that the vascular tree, in effect, is being reduced in size, the actual amount of fluid within the system is being increased. The kidney, of course, plays the leading part. It has been shown that with any type of fluid loss or volume depletion renal conservation of sodium occurs. Barger found sodium retention to be the first response to congestive failure in his experimental dogs (Barger *et al.*, 1959). Most workers believe that the first reaction is an increase in tubular reabsorption long before the glomerular filtration rate falls.

The latter, as measured, is usually unchanged, but the method is so crude that tiny decreases cannot be fully excluded.

In this regard it is worth digressing to mention that, although the role of aldosterone as a primary factor is not clear, it is essential in *permitting* renal tubular reabsorption of sodium if the stimulus for reabsorption is there (Ross, 1959). Its absence leads to loss of sodium even in congestive heart failure, but its presence does not guarantee that sodium retention will occur. Finally, with the usual reduction in glomerular filtration rate being much less than renal plasma flow, the filtration fraction is increased. There are some workers who believe that presentation of the highly osmotic post-glomerular blood to the tubules results in obligatory migration of water back into the tubular capillaries, and ultimately to fluid and sodium retention (Vander *et al.*, 1958).

Role of Hormones

The part played by hormones in the volume response to low cardiac output is much less certain than that of the kidney. Work during the past five years has established that aldosterone—a long-postulated but only recently isolated adrenal steroid—is salt-retaining through its action on the kidney tubule (Ross, 1959). Where aldosterone fits into the picture in congestive heart failure is not clear. In fact, it is not yet determined that aldosterone is really secreted in excess as a response to the failure state, and blocking of aldosterone by amphenone does not always induce sodium loss in congestive heart failure.

First of all, most findings of hyperaldosteronism have been made in patients *already* treated for congestive heart failure on a low-sodium diet and dehydrating regimen—proved stimuli for aldosterone secretion, even in the normal subject. Observations of free urinary aldosterone in a few patients with congestive heart failure prior to any therapy were made by Thorn's group (personal communication). They failed to demonstrate any consistent pattern, and, certainly, no striking elevation compared with the normal. Whether the inactive metabolic end-product, tetrahydroaldosterone, is elevated is as yet unknown. Indeed, some of the elevation in aldosterone level may be predicated on impaired hepatic detoxication, rather than a direct stimulus of the failure state itself.

Then, too, there exists the paradox that the salt-retaining hormone is secreted in response to any condition resulting in a decreased circulating blood volume, as with blood loss or dehydration. Congestive heart failure, on the other hand, predisposes to an *increased* blood volume—a situation known to inhibit aldosterone secretion. Aldosterone secretion has been shown to cease if the right atrium is distended, and to increase if the right atrium is deflated (Anderson *et al.*, 1959)—just the opposite of prevailing haemodynamic conditions in congestive heart failure. It has been suggested that although the venous volume is high the arterial tree is underfilled in congestive heart failure, but specific evidence for this is certainly lacking. Such could be an appealing explanation for the paradox of possibly increased aldosterone secretion in congestive heart failure.

In this regard, a specific neurovascular receptor has been found at the thyrocarotid arterial junction (Bartter *et al.*, 1960): aldosterone increasing with proximal constriction of the carotid artery. Whether this arterial

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hypovolaemia (perhaps in a local site in the vascular tree) is important in congestive heart failure, or possibly that the carotid receptor is *flow-sensitive*—that is, low carotid flow leading to activation of the reflex for increased aldosterone secretion—is unknown. Bartter's most recent work has shown that sodium depletion (and therefore volume depletion) resulted in a diminution in arterial pulse pressure, and suggests that this may activate aldosterone secretion (Gann *et al.*, 1960). Possibly diminution of pulse pressure in congestive heart failure may act similarly, although obviously at odds with the expanded fluid volume.

Finally, to resolve the paradox, it has been postulated that transudation of fluid into extravascular spaces, secondary to elevation of venous pressure, results in a so-called "vascular leak"—that this constant intravascular hypovolaemic feedback encourages aldosterone secretion. This would imply that aldosterone secretion in untreated congestive heart failure is a late and secondary participant in fluid accumulation, and only aggravates well-established biventricular failure with venous congestion.

There is some evidence, therefore, that in untreated failure aldosterone secretion may often be normal. On the other hand, it may be elevated, possibly owing to impaired hepatic detoxication, or in response to an arterial reflex, or owing to a secondary "vascular leak" if failure is so severe as to result in peripheral venous congestion. Most elevations in aldosterone probably occur in response to the physician's therapy itself. Here, a secondary homeostatic mechanism is activated to counteract iatrogenic interference with the primary homeostatic response to heart failure. A more complex feedback system cannot be imagined, and it is no wonder that the physiologists have yet to settle fully even the single fact of whether aldosterone is secreted in excess in response to congestive failure *per se*.

Pituitary antidiuretic hormone has been said to be increased in congestive heart failure. There is little evidence for this. Most studies, again, have suffered from a failure to carry out adequate measurements in the untreated state; from the fact that antidiuretic hormone detoxication may be incomplete owing to hepatic insufficiency; and, finally, because assay techniques are still inadequate. Antidiuretic hormone probably responds at least in normal fashion to renal and aldosterone effects on sodium—increased sodium levels will lead to water conservation. Its real importance, however, lies in the patient with severe congestive heart failure, usually with secondary complications—here, excessive antidiuretic hormone activity may result in massive water conservation, anasarca and dilution hyponatraemia, and concentrated urine (Weston *et al.*, 1958). This latter, however, may just be passive back-diffusion due to decreased glomerular filtration rate.

It is interesting to reflect on the fact that the various feedbacks act to expand intravascular volume only. This may be because, in the biological schema of things, most threats culminating in low cardiac output resulted from volume-depleting stimuli: exsanguination or dehydration. The response in an animal with a chronically inadequate blood flow may be handled by a similar indiscriminating mechanism, incapable of distinguishing the nature of the primary low output stimulus. On the other hand, as many workers have

emphasized, vascular volume accumulation, etc., does tend to increase cardiac diastolic filling pressure and volume. Through the Starling–Frank hypothesis, cardiac work can be increased somewhat, but only at an early stage in disease. That this should be wholly purposeful—to be teleological for a moment—seems somewhat untenable. Available to the bodily homeostasis, particularly to increase stroke output and heart rate, but *not* called upon in heart failure, are the sympathetic catecholamines. These have been shown to be present in adequate amounts in heart muscle as well as in other tissues, and heart muscle in failure often can still respond to these positive inotropic agents if given exogenously. The lack of increased catecholamine production or catechol-induced cardiac stimulation at any stage as part of the feedback to heart failure would belie "purpose." The value of fluid accumulation and the Starling principle in ultimate survival becomes questionable, particularly when the primary defect is low blood flow and not low blood volume.

Summary

Common to both congestive heart failure and to the various hypovolaemic states is an inadequate cardiac output. Probably acting through ancient feedback systems designed primarily to defend intravascular fluid volume against depletion, but sensitive in some way to a reduced output, fluid accumulation develops in congestive heart failure.

The first line of defence is a decrease in capacity of the reservoir of the vascular tree—that is, the systemic veins. This constriction is neurally mediated.

The second line of defence is renal conservation of sodium and water, primarily through increased tubular reabsorption, and possibly through imperceptibly decreased glomerular filtration rate. This response may be further abetted by the action of adrenal sodium-retaining hormone, a substance apparently more responsive to efforts at therapy than to the original disease itself. This response, unfortunately, can frustrate the very purpose of the programme of treatment.

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