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The Kidney in Heart Failure

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Renal dysfunction is a constant feature of congestive heart failure and is a stronger predictor of mortality than left ventricular ejection fraction or New York Heart Association classification. In heart failure, a reduction of glomerular filtration rate and renal plasma flow occurs, although the filtration fraction increases. There are many reason for this pattern. A reduction in effective circulating volume stimulates sympathetic activity and the renin-angiotensin-aldosterone system, and it is associated with increased concentrations of atrial natriuretic peptide, brain natriuretic peptide, and tumor necrosis factor α. Because in chronic kidney disease heart dysfunction commonly is present, an efficient cardiologist-nephrologist interaction should be promoted.
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The problem of heart failure is an old one. It is even discussed in the *Corpus Hippocraticum*, in which patients with shortness of breath, edema, anasarca, and cardiac cachexia are described.[1] Edema was thought to be caused by a shift of phlegm—a cold humor—from the brain into the chest. This theory persisted for a long time and finally came to an end with Andrea Cesalpino (1571, 1593) and William Harvey (1628).

Katz[2] provided a nice synopsis of the evolution of pathophysiology of heart failure over the past 2500 years. However, we disagree with him in his attribution to Harvey alone of the theory of hemodynamics. In fact, in *Quaestionum peripateticarum* (1571) and in *Quaestionum medicarum* (1593), Andrea Cesalpino of Arezzo (1524-1603) gave an exact demonstration of the general scheme of circulation.[3,4]

The crucial step in understanding the cardiorenal axis is represented by the studies of Starling,[5] who in the lectures to the Royal College of Surgeon in February 1896, stated that " as effect of heart failure sodium retention occurs along with reduced sodium excretion. Continuous increase in circulating fluid occurs till capillary pressure is restored." However, in 1931 Wollheim gave the first demonstration that blood volume increases with heart failure and edema, and in 1935 Peters[6] noted that "the kidneys react to changes of circulating blood but are indifferent to changes in the volume of body fluids." Shortly thereafter, it also became clear that in "heart disease there is inadequate translocation of fluid from venous to arterial side,"[7] and that the link between inadequate filling of the systemic arterial tree and edema formation is brought up by the kidneys.[8]

However, as pointed out by Anand,[9] "the effective blood volume is a poorly defined entity because there are no known mechanisms by which the body can directly monitor its inadequacy and it cannot be measured. Until we can measure effective blood volume this concept must remain hypothetic."

We now know that a reduction of effective circulating volume stimulates catecholamines, angiotensin II, endothelin, and anti diuretic hormone (ADH), which cause reduction of renal blood flow (RBF), glomerular filtration rate (GFR), and an increase of filtration fraction (FF). An increase in proximal reabsorption occurs, followed by reduced distal sodium delivery and activation of the juxtaglomerular apparatus.[10]

In 1946, Merrill[11] was the first to measure GFR and renal plasma flow (RPF) in heart failure (Fig 1) and it was evident that RPF was more affected than GFR. The information was confirmed by Aas and Blegen.[12] However, it took many more years and the advent of micropuncture techniques to understand the underlying tubular and glomerular mechanisms.[13,14]

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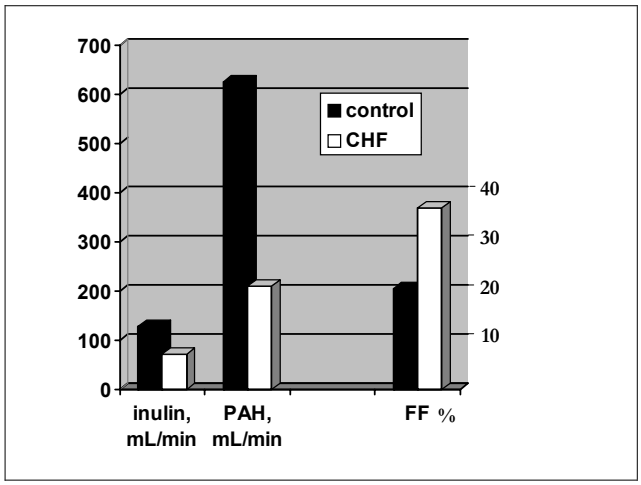

Figure 1 GFR, RPF, and FF. ■, control; □, CHF. Data from Merrill.[11]

Two Suicides

Andreoli[15] has shown nicely that in conditions of underfilling, similar to those occurring in systolic pump failure, a suicidal arterial filling takes place. In fact, because of the hemodynamic changes, there is an increase in afterload that leads to an increased end-diastolic volume. However, underfilling affects sodium avidity, thus increasing preload and causing an increase in end-diastolic volume, which reduces the ejection fraction.

The second suicide occurs via tumor necrosis factor α, which triggers apoptosis, increases nitric oxide, and enhances expression of proto-oncogenes. The synthesis of a locally active cytokine induces the heart to commit suicide at the molecular level.[16] In fact, tumor necrosis factor α causes cachexia, anorexia, and inflammation.

Neurohormonal Activation

Although kidney dysfunction at the present time is considered a general feature of congestive heart failure (CHF) it still is undecided[17] if it should be considered as a comorbidity or a maladaptation that induces changes of fluid regulation and the renin-angiotensin-aldosterone system (RAAS).

In CHF, significant changes occur in the cardiorenal axis, which operates under the control of the RAAS (sodium retaining, antidiuretic, vasoconstricting, and profibrotic), and of a group of peptides (atrial natriuretic peptide [ANP], brain natriuretic peptide [BNP], and C-type natriuretic peptide [CNP]). ANP and BNP, released by myocardial cells of the heart, and CNP, released by the endothelium, are natriuretic, diuretic, vasodilating, inhibitory for renin and aldosterone, and antifibrotic. In this context, ANP and BNP are seen as diuretic hormones secreted in response to stretch. ANP and BNP operate through guanylated cyclase A receptors, whereas CNP operates through a guanylate cyclase B receptor. All of them are bound to a clearance receptor that metabolizes them through the neutral endopeptidase. Blockade of neutral endopeptidase–receptor results in reduced GFR and reduced sodium excretion. ANP and BNP are considered markers of heart failure. BNP has a greater specificity and may be used for diagnostic purposes. It has been shown that in patients undergoing a 40% reduction of BNP concentration during treatment, this feature is associated with 1 class decrease in New York Heart Association (NYHA) classification of heart failure.[17]

Aldosterone is sodium retaining and potassium wasting, by acting on Nedd4, which causes sodium reabsorption. In CHF an aldosterone escape failure occurs, and aldosterone antagonists have many beneficial effects on sodium balance and heart fibrosis.[18]

ANP and BNP increase GFR by increasing glomerular hydrostatic pressure and Kf, decrease proximal and distal sodium reabsorption, increase blood flow in vasa recta, and decrease renin release. ANP and BNP blood concentrations are increased significantly in CHF. A decreased response to ANP has been shown in human beings with CHF. Hyporesponsiveness is of multifactorial origin, and includes a reduction of renal perfusion pressure and an increase in renal sympathetic activity. Finally, it should be stressed that in CHF the kidneys are normal, and, when transplanted in healthy individuals, they operate normally.

Taken together, the neurohormonal response activated in CHF is identical to that which occurs after physical exercise or hemorrhage.[19,20] A response evolved over the millennia to resist those life-threatening conditions such as hemorrhage and physical exercise. Under these conditions there is an increased sympathetic activity with venoconstriction, tachycardia, myocardial stimulation, and regional vasoconstriction.[9] Additionally, in CHF the threat to blood pressure is long lasting, therefore the effector mechanism is operating continuously, thus the unloading of high-pressure baroreceptors stimulate sympathetic activity, as well as the RAAS and Arginine Vasopressin (AVP).

GFR and Starling Forces

The transcapillary hydrostatic pressure (ΔP) slowly decreases along the capillary length both in health and heart failure. However, in CHF it is much higher than in normal patients because of efferent arterial vasoconstriction. The transmural oncotic pressure ($\Delta\pi$) increases over the capillary length both in normal patients and patients with CHF. However, in CHF it also is higher because of the increase in FF. This situation is brought about by a disproportionate increase in efferent vasoconstriction that protects GFR.

Along the peritubular capillary, ΔP is reduced more than in normal subjects. However, $\Delta\pi$ is higher, thus the driving force ($\Delta P - \Delta\pi$) enhances proximal reabsorption of sodium and water. However, in CHF the changes in intrarenal hemodynamics, the sympathetic stimulation, and the stimulation of angiotensin II also may promote sodium reabsorption in Henle's loop.[21]

The afferent to efferent balance is shown in Figure 2, which gives a synopsis of RBF and GFR in treated and untreated heart failure patients.[22] It should be added that patients with end-stage heart failure treated with angiotensin-converting