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Mina Rizk Aziz

PHYSIOLOGICAL RELATIONSHIP BETWEEN HEART AND KIDNEY

The heart and the kidneys share responsibility for maintaining hemodynamic stability and end-organ perfusion through a tight-knit relationship that controls cardiac output, volume status, and vascular tone. Connections between these organs ensure that subtle physiologic changes in one system are tempered by compensation in the other. As such, hemodynamic control remains stable through a wide range of physiologic conditions ***(Tang and Mullen et al., 2010)*** **.**

Communication between the heart and kidneys occurs through a variety of pathways. These include perfusion pressure, filling pressure, and neurohormonal activity. In particular some of the key mediators include the sympathetic nervous system, the renin-angiotensin-aldosterone axis, and atrial natriuretic peptide. These agents have receptors in the heart, the kidneys, and the vasculature that affect volume status, vascular tone, cardiac output, and inotropy. A change in the performance of one of these organs elicits a cascade of mediators that affects the other**.** ***(Ronco et al., 2010.)***

Mediators Of Cadiorenal Syndrome:

There are a variety of neurohormonal mediators associated with the deterioration of kidney function in acute decomensated heart failure (ADHF) Understanding these mediators and effectors yields insight into the diagnosis and therapy of CRS. ***(Geisberg and Butler 2006).***

The kidneys produce a glomerular filtrate that is dependent upon perfusion pressure and afferent and efferent arteriolar tone. The arteriolar resistance is under intrinsic myogenic control, and responsive to several neurohormonal systems***. (Geisberg and Butler 2006).***

The renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and local vasodilators such as nitric oxide (NO), adenosine, and prostaglandins contribute to maintaining the glomerular filtration rate (GFR) through conditions of increased or decreased perfusion pressure .When renal perfusion pressure decreases, angiotensin II (AII) preferentially increases the efferent arteriolar resistance to preserve intraglomerular hydrostatic pressure and maintain GFR. Simultaneously, the afferent arteriole, under control of tubuloglomerular feedback and prostaglandins, dilates to increase the transmission of perfusion pressure into the glomerulus. ***(Geisberg and Butler 2006).***

1- Renin-Angiotensin-Aldosterone System:

The renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates blood pressure and water (fluid) balance**.**

When renal blood flow is reduced, juxtaglomerular cells in the kidneys activate their prorenin and secrete renin directly into circulation. Plasma renin then carries out the conversion of angiotensinogen released by the liver to angiotensin I. ***(Kumar et al., 2010).***

Angiotensin I is subsequently converted to angiotensin II by the enzyme angiotensin-converting enzyme found in the lungs. Angiotensin II is a potent vaso-active peptide that causes blood vessels to constrict, resulting in increased blood pressure**. *(Yee et al., 2010).***

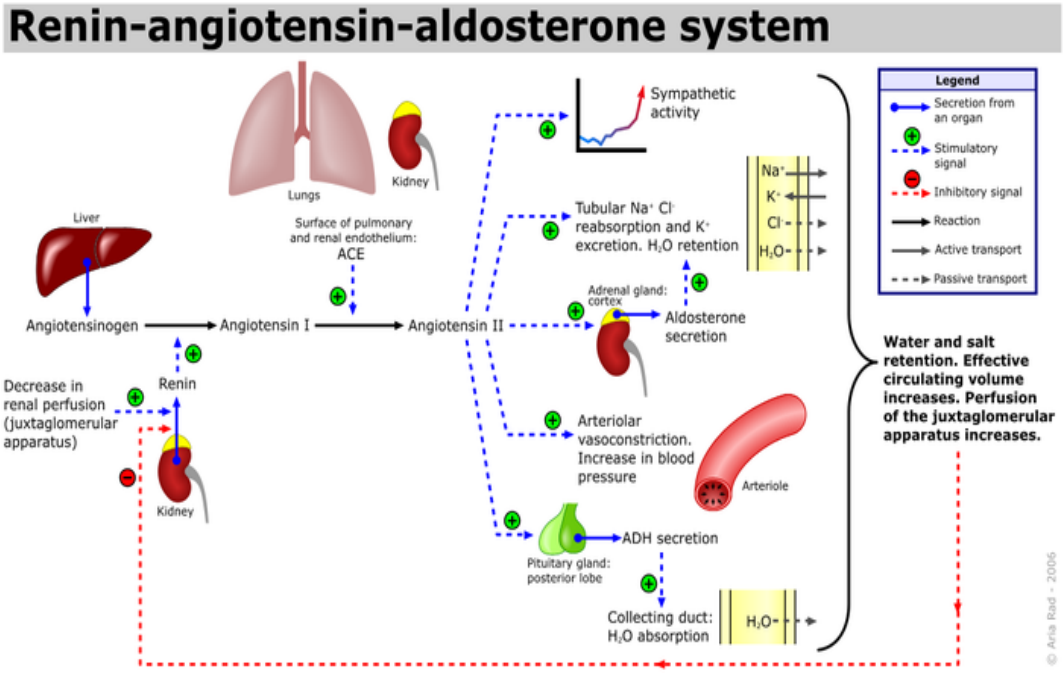
Angiotensin II also stimulates the secretion of the hormone aldosterone from the adrenal cortex. Aldosterone causes the tubules of the kidneys to increase the reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases blood pressure. ***(Yee et al., 2010).***

The system can be activated when there is a loss of blood volume or a drop in blood pressure (such as in hemorrhage or dehydration). This loss of pressure is interpreted by baroreceptors in the carotid sinus. In alternative fashion, a decrease in the filtrate NaCl concentration and/or decreased filtrate flow rate will stimulate the macula densa to signal the juxtaglomerular cells to release renin**.*(Paul et al., 2006).***

If the perfusion of the juxtaglomerular apparatus in the kidney's macula densa decreases, then the juxtaglomerular cells (granular cells, modified pericytes in the glomerular capillary) release the enzyme renin. Renin cleaves a zymogen, an inactive peptide, called *angiotensinogen*, converting it into *angiotensin I.* Angiotensin I is then converted to *angiotensin II* by angiotensin-converting enzyme (ACE), which is thought to be found mainly in lung capillaries. ***(Paul et al., 2006).***

Angiotensin II is the major bioactive product of the renin-angiotensin system, binding to receptors on intraglomerular mesangial cells, causing these cells to contract along with the blood vessels surrounding them and

causing the release of aldosterone from the zona glomerulosa in the adrenal cortex. Angiotensin II acts as an endocrine, autocrine paracrine and intracrine hormone . ***(Solomon et al., 2005).***



Figure(1): Renin-angiotensin-aldosteron system .***(Yee et al., 2005).***

Cardiovascular effect : It is believed that angiotensin I may have some minor activity, but angiotensin II is the major bio-active product. Angiotensin II has a variety of effects on the body: Throughout the body, it is a potent vasoconstrictor of arterioles. **In the kidneys**, AII constricts glomerular arterioles, having a greater effect on efferent arterioles than afferent. As with most other capillary beds in the body, the constriction of afferent arterioles increases the arteriolar resistance, raising systemic arterial blood pressure and decreasing the blood flow. However, the kidneys must continue to filter enough blood despite this drop in blood flow, necessitating mechanisms to keep glomerular blood pressure up. To do this,

angiotensin II constricts efferent arterioles, which forces blood to build up in the glomerulus, increasing glomerular pressure**. *(Solomon et al., 2005).***

The glomerular filtration rate (GFR) is thus maintained, and blood filtration can continue despite lowered overall kidney blood flow. Because the filtration fraction has increased, there is less plasma fluid in the downstream peritubular capillaries. This in turn leads to a decreased hydrostatic pressure and increased oncotic pressure (due to unfiltered plasma proteins) in the peritubular capillaries. The effect of decreased hydrostatic pressure and increased oncotic pressure in the peritubular capillaries will facilitate increased reabsorption of tubular fluid.***(Kobori et al., 2007).***

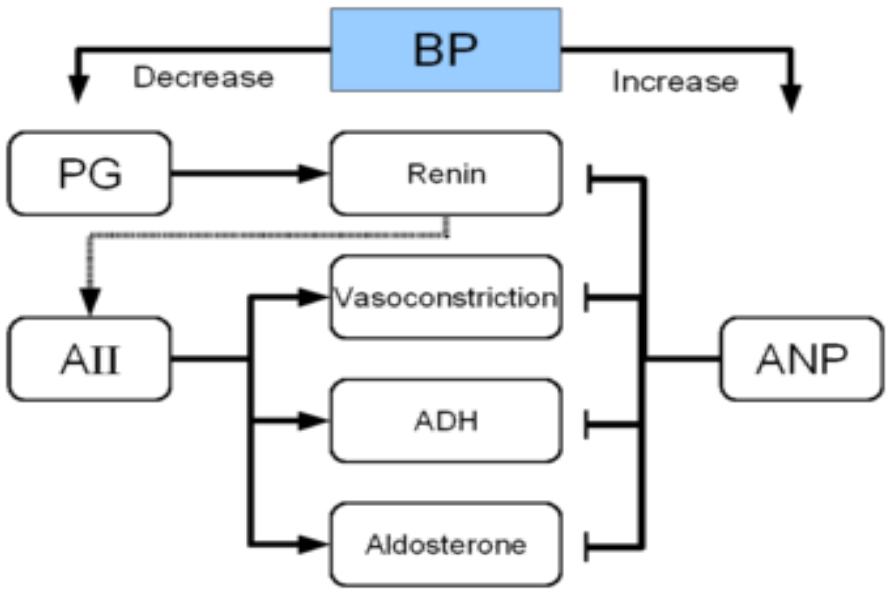
Angiotensin II decreases medullary blood flow through the vasa recta. This decreases the washout of NaCl and urea in the kidney medullary space. Thus, higher concentrations of NaCl and urea in the medulla facilitate increased absorption of tubular fluid. Furthermore, increased reabsorption of fluid into the medulla will increase passive reabsorption of sodium along the thick ascending limb of the loop of Henle. ***(Solomon et al., 2005).***

Angiotensin II stimulates Na^+/H^+ exchangers located on the apical membranes (faces the tubular lumen) of cells in the proximal tubule and thick ascending limb of the loop of Henle in addition to Na^+ channels in the collecting ducts. This will ultimately lead to increased sodium reabsorption Angiotensin II stimulates the hypertrophy of renal tubule cells, leading to further sodium reabsorption. .***(Kobori et al., 2007).***

In the adrenal cortex, it acts to cause the release of aldosterone. Aldosterone acts on the tubules (e.g., the distal convoluted tubules and the cortical collecting ducts) in the kidneys, causing them to reabsorb

more sodium and water from the urine. This increases blood volume and, therefore, increases blood pressure. In exchange for the reabsorbing of sodium to blood, potassium is secreted into the tubules, becomes part of urine and is excreted. ***(Yee et al., 2010) .***

Release of anti-diuretic hormone (ADH), also called vasopressin – ADH is made in the hypothalamus and released from the posterior pituitary gland. As its name suggests, it also exhibits vaso-constrictive properties, but its main course of action is to stimulate reabsorption of water in the kidneys. ADH also acts on the central nervous system to increase an individual's appetite for salt, and to stimulate the sensation of thirst. These effects directly act together to increase blood pressure and are opposed by atrial natriuretic peptide (ANP**) *(Yee et al., 2010).***



Figure(2): Effect of blood pressure on hormone relase(www.wikipedia.org wiki renal hormone regulation 2010)

Local rennin-angiotensin system:

Locally expressed renin-angiotensin systems have been found in a number of tissues, including the kidneys, adrenal glands, the heart, vasculature and nervous system, and have a variety of functions, including local cardiovascular regulation, in association or independently of the systemic renin-angiotensin system, as well as non-cardiovascular functions***.(Paul et al., 2006).***

Outside the kidneys, renin is predominantly picked up from the circulation but may be secreted locally in some tissues, its precursor prorenin is highly expressed in tissues and more than half of circulating prorenin is of extrarenal origin, but its physiological role besides serving as precursor to renin is still unclear***.(Nguyen , 2011).***

In the adrenal glands, it is likely involved in the paracrine regulation of aldosterone secretion, in the heart and vasculature, it may be involved in remodeling or vascular tone, and in the brain where it is largely independent of the circulatory RAS, it may be involved in local blood pressure regulation.***(Paul et al., 2006).***

Thus AII seems to play a direct role in renal injury and direct damage to the glomerular filtration barrier .***(Kobori et al., 2007).***

2-Species Nitric oxide and Reactive Oxygen Disequilibrium

Nitric oxide, an endothelium-derived relaxing factor, is a vasodilator that acts to regulate vascular tone, blood pressure, and smooth muscle hypertrophy through down regulation of ACE and the AII type 1 receptor. NO therefore represents a physiologic antagonist of AII at both the glomerular and tubular levels . It also plays a role in tubuloglomerular feedback through dilation of the afferent arteriole . ***(Bataineh et al., 1998).***

In decompensated heart failure, RAAS activation causes angiotensin mediated hypertension through increased systemic vascular resistance, greater renal perfusion pressure through preferential efferent arteriolar vasoconstriction , and renal oxidative stress through NADPH-oxidase activity .***(Kielstein, et al., 2003).***

Even mild heart failure is associated with decreased renal perfusion by way of NO inhibition. Also, Endothelin I (ET 1) is implicated in vasoconstriction, causing mesangial cell contraction and mesangial cell mitogenesis . Whereas AII stimulates the release of ET 1, NO inhibits ET 1 release from endothelial cells. An imbalance in favor of more ET 1 production causes endothelial dysfunction as well as glomerular and interstitial damage **.*(Kielstein, et al., 2003).***

3-Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) :

Atrial natriuretic peptide (ANP), atrial natriuretic factor (ANF), atrial natriuretic hormone (ANH) ,Cardionatrine, Cardiodilatine (CDD) or

atriopeptin, is a powerful vasodilator, and a protein (polypeptide) hormone secreted by heart muscle cells. ***(Widmaier et al., 2008).***

Three distinct NPs (A-type, B-type, and C-type) are known to circulate in humans. Three NP receptors (NPR-A, NPR-B, NPR-C) are responsible for activating the cyclic-guanosine monophosphate (cGMP)-dependent signaling cascades. NPs convey a multitude of actions on the cardiovascular system including vascular smooth muscle cell relaxation, promotion of natriuresis, as well as direct myocardial effects. In concert, NPs achieve a more favorable neurohormonal and hemodynamic state ANP is stored in preformed granules in atrial tissue. B-type NP (BNP) is predominantly synthesized from increased wall stress. Its concentration is highest in atrial tissue, however more is released from the ventricles owed to its greater mass. C-type NP (CNP) is primarily released by the central nervous tissue, vascular endothelium and in minute amounts by cardiac tissues***.(Potter et al., 2009).***

It is involved in the homeostatic control of body water, sodium, potassium and fat (adipose tissue). It is released by muscle cells in the upper chambers (atria) of the heart (atrial myocytes) in response to high blood volume. ANP acts to reduce the water, sodium and adipose loads on the circulatory system, thereby reducing blood pressure.. ANP has exactly the opposite function of the aldosterone secreted by the zona glomerulosa in regard to its effect on sodium in the kidney - that is, aldosterone stimulates sodium retention and ANP generates sodium loss***. (Potter et al., 2009).***

ANP is produced, stored, and released mainly by cardiac myocytes of the atria of the heart. Synthesis of ANP also takes place in the ventricles, brain, suprarenal glands, and renal glands. It is released in response to atrial

stretch and a variety of other signals induced by hypervolemia, exercise, or caloric restriction. ***(Widmaier et al., 2008).***

The hormone is constitutively expressed in the ventricles in response to stress induced by increased afterload (e.g. increased ventricular pressure from aortic stenosis) or injury (e.g. myocardial infarction).

ANP is secreted in response to: ***(Widmaier et al., 2008).***

- Atrial distention, stretching of the vessel walls
- Sympathetic stimulation of β-adrenoceptors
- Raised sodium concentration (hypernatremia), though sodium concentration is not the direct stimulus for increased ANP secretion
- Angiotensin-I
- Endothelin, a potent vasoconstrictor

The atria become distended by high extracellular fluid and blood volume, and atrial fibrillation. It should be noted that ANP secretion increases in response to immersion of the body in water, which causes atrial stretch due to an altered distribution of intravascular fluid***. (Widmaier et al., 2008).***

Renal effect Dilates the afferent glomerular arteriole, constricts the efferent glomerular arteriole, and relaxes the mesangial cells. This increases pressure in the glomerular capillaries, thus increasing the glomerular filtration rate (GFR), resulting in greater excretion of sodium and water***. (Potter et al., 2009).***

Increases blood flow through the vasa recta, which will wash the solutes (NaCl and urea) out of the medullary interstitium. The lower osmolarity of the medullary interstitium leads to less reabsorption of tubular

fluid and increased excretion**.** Decreases sodium reabsorption in the distal convoluted tubule and cortical collecting duct of the nephron via guanosine 3',5'-cyclic monophosphate (cGMP) dependent phosphorylation of epithelial sodium channel (ENaC), Inhibits renin secretion, thereby inhibiting the renin-angiotensin-aldosterone system.and reduces aldosterone secretion by the adrenal cortex***. (Potter et al., 2009).***

Atrial natriuretic peptide (ANP) increases Na^+ excretion by decreasing the amount of Na^+ reabsorbed from the inner medullary collecting duct via a decrease in the permeability of the apical membrane of the collecting duct epithelial cells. Less Na^+ is able to enter the epithelial cells and, therefore, less Na^+ is reabsorbed. ANP also increases Na^+ excretion by increasing the filtered load of Na^+. ***(Potter et al., 2009).***

Vascular effect Relaxes vascular smooth muscle in arterioles and venules by: Membrane Receptor-mediated elevation of vascular smooth muscle cGMP and inhibition of the effects of catecholamines. ***(Potter et al., 2009).***

Cardiac effect Normally, the cross-talk between the heart and the kidneys occurs through atrial-renal reflexes which contribute to maintaining the total body volume in the normal range. ***(Schrier, 2006).***

In a nonfailing heart, any increase in atrial pressure diminishes the arginine vasopressin release (AVP) through the Henry- Gauer Reflex, decreases renal sympathetic tone and increases the atrial natriuretic peptide **,** all of which increase the urinary sodium and water excretion rate. In HF, however, there is blunting of these reflexes in the low-pressure circulation,

probably secondary to being over ridden by reflexes initiated in the high-pressure arterial circulation. ***(Schrier , 2006).***

4-Erythropoietin:

Is a glycoprotein hormone that controls erythropoiesis, or red blood cell production. It is a cytokine (protein signaling molecule) for erythrocyte (red blood cell) precursors in the bone marrow. .Also called hematopoietin or hemopoietin, it is produced by interstitial fibroblasts in the kidney in close association with peritubular capillary and tubular epithelial tubule. It is also produced in perisinusoidal cells in the liver. While liver production predominates in the fetal and perinatal period, renal production is predominant during adulthood***.(Verhaar et al., 2003).***

The primary role of erythropoietin is an essential hormone for red cell production. Without it, definitive erythropoiesis does not take place. Under hypoxic conditions, the kidney will produce and secrete erythropoietin to increase the production of red blood cells . Erythropoietin has its primary effect on red blood cell progenitors and precursors (which are found in the bone marrow in humans) by promoting their survival through protecting these cells from apoptosis. ***.(Verhaar et al., 2003).***

Erythropoietin has non-erythropoietic effects that could be seen in a protective role at vascular diseases, lowering the zone of ischemia (for example at heart failure and cerebral vascular failure) protection of apoptosis through its antioxidant characteristics, and proangiogenic potential with positive remodeling of myocardium ,vasoconstriction-dependent hypertension , stimulating angiogenesis,. and inducing proliferation of smooth muscle fibers**.. *(Van der Meer et al., 2004).***

Erythropoietin production is regulated by negative reversed power through oxygen concentration in the blood. As a response on hypoxia, kidneys produce a large quantity of Erythropoietin and in that way contribute to increasing of the number of erythrocytes, and by that improve supplying oxygen to the tissue***. (Van der Meer et al., 2004).***

5-Antidiuretic hormone (ADH):

Vasopressin, also known as arginine vasopressin (AVP) or argipressin, is a neurohypophysial hormone. . It is derived from a preprohormone precursor that is synthesized in the hypothalamus and stored in vesicles at the posterior pituitary. Most of it is stored in the posterior pituitary to be released into the bloodstream. However, some AVP may also be released directly into the brain, .***(Caldwell et al.,2006).***

Its two primary functions are to retain water in the body and to constrict blood vessels. Vasopressin regulates the body's retention of water by acting to increase water reabsorption in the collecting ducts of the kidney nephron. ***.(Sands et al., 2011).***

Vasopressin is a peptide hormone that increases water permeability of the kidney's collecting duct and distal convoluted tubule. It also increases peripheral vascular resistance, which in turn increases arterial blood pressure. It plays a key role in homeostasis, by the regulation of water, glucose, and salts in the blood .***(Caldwell et al.,2006).***

One of the most important roles of AVP is to regulate the body's retention of water; it is released when the body is dehydrated and causes the kidneys to conserve water, thus concentrating the urine and reducing urine