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The Kidney as a Master Regulator of Blood Pressure and Cardiac Function: A Comprehensive Review

Subhadeep Aditya

MSc Biotechnology, Healthcare Consultant
Email: *mrsubhadeep[at]proton.me*

Abstract: ***Background: The kidneys occupy a central position in cardiovascular homeostasis through their multifaceted roles in fluid and electrolyte regulation, hormonal signaling, and sympathetic modulation. Dysfunction in renal physiology is among the strongest independent predictors of hypertension and adverse cardiac outcomes. Methods: This narrative review synthesizes evidence from original research articles, systematic reviews, and meta-analyses published between 2000 and 2024 in PubMed, MEDLINE, and Cochrane databases, focusing on renal mechanisms governing blood pressure and cardiac function. Results: Evidence demonstrates that the kidney regulates blood pressure through sodium handling, the renin-angiotensin-aldosterone system (RAAS), tubuloglomerular feedback, and renal sympathetic innervation. Cardiorenal syndrome (CRS) describes a spectrum of bidirectional pathophysiology in which cardiac dysfunction impairs renal function and vice versa. Key mediators include angiotensin II, aldosterone, erythropoietin, fibroblast growth factor-23 (FGF-23), and natriuretic peptides. Conclusion: A thorough understanding of cardiorenal physiology is essential for clinicians managing hypertension, heart failure, and chronic kidney disease. Integrated therapeutic strategies targeting RAAS, sympathetic activity, and sodium balance confer significant cardiovascular and renoprotective benefits.***

Keywords: kidney; blood pressure; cardiac function; renin-angiotensin-aldosterone system; cardiorenal syndrome; hypertension; heart failure; sodium homeostasis

1. Introduction

The kidney is far more than an organ of waste excretion. It is a sophisticated homeostatic organ whose influence pervades virtually every dimension of cardiovascular physiology. Blood pressure- the hydrostatic force driving systemic circulation- is ultimately determined by cardiac output and total peripheral vascular resistance, but the kidney occupies an irreplaceable regulatory position through its continuous adjustment of circulating blood volume, osmolality, and vasoactive hormone levels.

Long-chain connections between renal and cardiac physiology have been recognized since the pioneering work of Bright in 1836, who first noted hypertrophy of the heart in patients with renal disease. Over the ensuing two centuries, molecular and clinical research has elaborated the remarkable complexity of renal-cardiovascular crosstalk. Today, cardiorenal syndrome (CRS) is a recognized clinical entity encompassing five subtypes that reflect acute and chronic, forward and reverse, interactions between the heart and kidneys.

Globally, hypertension affects approximately 1.28 billion adults and is the single largest attributable risk factor for cardiovascular disease and premature death. Chronic kidney disease (CKD) affects an estimated 850 million individuals worldwide and independently multiplies cardiovascular risk two- to fourfold at every stage. Understanding the mechanistic links is not merely of academic interest: it is the foundation for rational, evidence-based treatment of both conditions.

This review examines the principal pathways by which the kidney governs blood pressure and supports cardiac function, delineates the pathophysiology of cardiorenal interactions, and surveys current therapeutic strategies that harness these pathways to reduce cardiorenal morbidity and mortality.

2. Renal Anatomy Relevant to Cardiovascular Regulation

Each kidney contains approximately one million nephrons, the functional units responsible for filtration, reabsorption, and secretion. The nephron comprises the glomerulus- a tuft of fenestrated capillaries enclosed within Bowman's capsule- and a tubular system subdivided into the proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting duct.

Glomerular filtration rate (GFR), normally 90–120 mL/min/1.73 m^2 in adults, is primarily a function of glomerular capillary pressure, oncotic pressure, and the filtration coefficient. The renal vasculature — comprising afferent and efferent arterioles- is uniquely configured to exert exquisitely precise autoregulatory control over glomerular capillary pressure and, consequently, over whole-body blood pressure.

The juxtaglomerular apparatus (JGA), located at the vascular pole of each glomerulus, is pivotal to blood pressure regulation. Renin-secreting granular cells in the afferent arteriolar wall respond to reduced stretch (falling renal perfusion pressure), reduced tubular chloride delivery (sensed by the macula densa), and sympathetic stimulation via beta-1 adrenoceptors. The JGA thus serves as an exquisitely sensitive baroreceptor and chemoreceptor, translating local renal perfusion signals into systemic hormonal responses.

3. Renal Mechanisms of Blood Pressure Regulation

3.1 Pressure-Natriuresis and the Guyton Paradigm

The foundational principle of long-term blood pressure regulation was articulated by Arthur Guyton and colleagues in the 1970s. The "pressure-natriuresis" relationship describes the kidney's intrinsic tendency to increase sodium and water excretion in response to elevated arterial pressure, thereby reducing blood volume, cardiac output, and ultimately restoring blood pressure toward the set point. Guyton argued that the renal-body fluid feedback loop is the only mechanism capable of achieving sustained, infinite-gain regulation of arterial pressure. Any perturbation that resets the pressure-natriuresis relationship- whether intrinsic renal disease, hormonal excess, or pharmacological manipulation- will produce a new long-term steady-state arterial pressure.

Clinical corroboration of this model comes from the observation that virtually all forms of chronic hypertension involve impaired renal sodium excretion at normal blood pressures. The kidneys of hypertensive patients exhibit a rightward shift in the pressure-natriuresis curve, requiring higher than normal arterial pressures to maintain sodium balance.

3.2 Sodium and Volume Homeostasis

Sodium balance is the primary determinant of extracellular fluid (ECF) volume and, consequently, of blood pressure. The kidneys filter approximately 25,000 mmol of sodium daily, reabsorbing greater than 99% of this load through a hierarchy of transporter systems distributed along the nephron.

In the proximal tubule, the sodium-hydrogen exchanger 3 (NHE3) and sodium-glucose co-transporter 2 (SGLT2) reclaim roughly 60–65% of filtered sodium. In the thick ascending limb of Henle, the Na-K-2Cl co-transporter (NKCC2)- the target of loop diuretics- handles approximately 25%. In the distal nephron and collecting duct, aldosterone-stimulated epithelial sodium channels (ENaC) finely tune final sodium excretion. These transporters are regulated by angiotensin II, aldosterone, natriuretic peptides, catecholamines, and insulin, among others, integrating cardiovascular and metabolic signals to maintain precise sodium balance.

3.3 The Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS constitutes the most powerful endocrine cascade in blood pressure regulation. Renin, an aspartyl protease secreted by juxtaglomerular cells, cleaves angiotensinogen (synthesized by the liver) to produce the decapeptide angiotensin I (Ang I). Angiotensin-converting enzyme (ACE), expressed abundantly on the pulmonary endothelium, converts Ang I to the octapeptide angiotensin II (Ang II).

Ang II exerts its primary cardiovascular effects through AT1 receptors, mediating vasoconstriction of systemic and renal arterioles, stimulation of adrenal aldosterone release, sodium retention in the proximal tubule, sympathetic facilitation, and myocardial hypertrophy and fibrosis. The net result is an increase in blood pressure, cardiac afterload, and extracellular fluid volume. AT2 receptors, by contrast, broadly oppose AT1-mediated effects, promoting vasodilation, natriuresis, and apoptosis; their functional significance is enhanced by pharmacological AT1 blockade.

Aldosterone, released from the adrenal zona glomerulosa in response to Ang II and hyperkalemia, binds mineralocorticoid receptors in the collecting duct principal cells, upregulating ENaC and Na-K-ATPase expression. The resulting sodium retention and potassium excretion amplify the blood pressure and volume-expanding effects of RAAS activation. Importantly, aldosterone also exerts direct, non-epithelial effects on the heart and vasculature, promoting inflammation, oxidative stress, and fibrosis- effects that contribute to adverse cardiac remodeling independent of blood pressure.

3.4 Tubuloglomerular Feedback

Tubuloglomerular feedback (TGF) is an intrarenal autoregulatory mechanism that couples GFR to the rate of solute delivery at the macula densa. Increased NaCl concentration at the macula densa triggers afferent arteriolar constriction via adenosine release, reducing GFR. This system prevents excessive tubular solute loads and modulates renal blood flow, contributing to the intrinsic autoregulatory capacity of the kidney to stabilize GFR and sodium excretion across a wide range of perfusion pressures.

3.5 Renal Sympathetic Nervous System

The kidneys receive dense sympathetic innervation from the celiac and superior mesenteric ganglia. Renal sympathetic nerve activity (RSNA) modulates all three major determinants of blood pressure and volume regulation: it stimulates renin secretion (beta-1 adrenoceptors), promotes tubular sodium reabsorption (alpha-1B adrenoceptors), and reduces renal blood flow through afferent arteriolar vasoconstriction.

Pathological augmentation of RSNA has been demonstrated in essential hypertension, obesity-related hypertension, CKD, and heart failure. Afferent renal nerve fibers, which project to hypothalamic cardiovascular centers, may play an equally important amplifying role: renal sensory information dysregulates central sympathetic outflow, creating a vicious cycle. This pathophysiological understanding underpins the rationale for catheter-based renal denervation as a treatment modality for resistant hypertension.

3.6 Natriuretic Peptides and Renal Counter-Regulation

The natriuretic peptide family- atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP)- constitutes the principal hormonal counterpart to RAAS activation. ANP is released from atrial myocytes in response to atrial wall stretch, and BNP from ventricular myocytes in response to increased ventricular end-diastolic pressure. Both peptides act on the kidney to increase GFR, inhibit renin and aldosterone secretion, and directly inhibit tubular sodium reabsorption. They additionally exert vasodilatory, anti-inflammatory, and anti-fibrotic effects on the cardiovascular system.

In heart failure, circulating BNP and its cleavage product NT-proBNP rise dramatically and serve as established biomarkers of hemodynamic stress and prognosis. However, in advanced heart failure and CKD, resistance to natriuretic peptide signaling develops, contributing to persistent volume overload despite elevated peptide levels.

4. Cardiorenal Interactions and the Cardiorenal Syndrome

4.1 Classification of Cardiorenal Syndrome

The Acute Dialysis Quality Initiative (ADQI) has defined cardiorenal syndrome as a pathophysiological disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction of the other. Five subtypes are recognized based on the sequence and acuity of organ involvement:

Table 1: Classification of Cardiorenal Syndrome (ADQI Consensus)

Type	Name	Description
CRS Type 1	Acute Cardiorenal	Acute cardiac dysfunction (e.g., acute decompensated heart failure, cardiogenic shock) causing acute kidney injury (AKI)
CRS Type 2	Chronic Cardiorenal	Chronic cardiac dysfunction (e.g., chronic heart failure) causing progressive CKD
CRS Type 3	Acute Renocardiac	Acute kidney dysfunction causing acute cardiac injury or dysfunction
CRS Type 4	Chronic Renocardiac	Chronic kidney disease contributing to decreased cardiac function, LV hypertrophy, or increased risk of adverse cardiovascular events
CRS Type 5	Secondary CRS	Systemic conditions (e.g., diabetes, amyloidosis, sepsis) causing both cardiac and renal dysfunction simultaneously

4.2 Hemodynamic Mechanisms

Reduced cardiac output in heart failure directly impairs renal perfusion through two principal hemodynamic pathways. First, forward failure- decreased stroke volume and cardiac output — reduces renal artery perfusion pressure, activating RAAS and sympathetic responses that initially attempt to maintain GFR through efferent arteriolar constriction, but eventually produce ischemic renal dysfunction. Second, backward failure — elevated central venous pressure transmitted to the renal venous system - increases renal interstitial pressure, compresses peritubular capillaries, and directly impairs glomerular filtration by reducing the net filtration pressure.

Clinical and experimental data increasingly support elevated venous pressure as a dominant mechanism of cardiorenal dysfunction in acute decompensated heart failure, with venous congestion correlating more strongly with worsening renal function than reduced cardiac index. This paradigm has shifted therapeutic emphasis toward decongestion as a primary renoprotective strategy.

4.3 Neurohormonal and Inflammatory Mechanisms

Beyond hemodynamic factors, a cascade of neurohormonal and inflammatory mediators perpetuates cardiorenal injury. Ang II, in addition to promoting vasoconstriction and sodium retention, stimulates mesangial cell proliferation, activates transforming growth factor-beta (TGF-β) signaling, and drives glomerulosclerosis. In the myocardium, Ang II and aldosterone independently promote interstitial fibrosis, impair diastolic relaxation, and precipitate arrhythmias.

Fibroblast growth factor-23 (FGF-23), a phosphaturic hormone produced by osteocytes and chronically elevated in CKD, has emerged as an important cardiorenal mediator. FGF-23 directly induces left ventricular hypertrophy (LVH) through a klotho-independent mechanism, independent of its phosphaturic effects. Elevated FGF-23 levels powerfully predict cardiovascular events and mortality in CKD patients. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase accumulating in CKD, contributes to endothelial dysfunction, hypertension, and accelerated atherosclerosis.

5. The Kidney in Hypertension

5.1 Primary Hypertension

Essential hypertension, accounting for 90–95% of cases, is characterized by impaired renal sodium excretion at normal blood pressures- a pathological rightward shift in the pressure-natriuresis relationship. Susceptibility genes affecting tubular sodium transporters (particularly NHE3 and ENaC), RAAS components, adducin, and sympathoadrenal signaling have been identified in genome-wide association studies (GWAS). Environmental factors- dietary sodium excess, obesity, insulin resistance, and psychosocial stress — interact with this polygenic background to produce sustained hypertension.

The kidney is simultaneously victim and perpetuator of hypertension. Sustained elevations in blood pressure cause hypertensive nephropathy through arterionephrosclerosis, impaired renal autoregulation, and glomerular hypertension, progressively reducing nephron number and functional reserve. The resultant further impairment of sodium excretion drives blood pressure still higher, establishing a self-amplifying cycle of progressive renal and cardiovascular damage.

5.2 Renovascular Hypertension

Renovascular hypertension (RVH) results from unilateral or bilateral renal artery stenosis (RAS), typically due to atherosclerosis (80–90%) or fibromuscular dysplasia (10–20%). Reduced renal perfusion pressure distal to the stenosis activates the JGA, markedly increasing renin and Ang II production. In unilateral RAS (two-kidney, one-clip model), the contralateral kidney responds with pressure-natriuresis until Ang II levels suppress its renin secretion; hypertension is volume-mediated and renin-dependent. In bilateral RAS, pressure-natriuresis is globally impaired, and hypertension becomes volume-dependent with suppressed renin levels- an

important distinction with diagnostic and therapeutic implications.

5.3 CKD-Associated Hypertension

Hypertension is both the most common complication and a major driver of CKD progression. In CKD, mechanisms driving hypertension include enhanced tubular sodium reabsorption (partly mediated by increased RAAS activity), reduced GFR and nephron mass, augmented sympathetic nervous system activity (partly driven by afferent renal nerve signaling), endothelial dysfunction from oxidative stress and ADMA accumulation, and impaired natriuretic peptide responsiveness.

Blood pressure control in CKD slows progression to end-stage renal disease (ESRD) and reduces cardiovascular events. Target blood pressure in patients with proteinuric CKD is currently recommended at less than 130/80 mmHg by international guidelines (JNC 8, ESC/ESH 2023, KDIGO 2021).

6. Direct Renal Effects on Cardiac Structure and Function

6.1 Left Ventricular Hypertrophy

LVH is the most prevalent cardiac complication of CKD, present in approximately 75% of patients initiating dialysis and 40% of those with moderate CKD. Its pathogenesis is multifactorial, driven by pressure overload (hypertension), volume overload (sodium and water retention), and direct hormonal signals including Ang II, aldosterone, FGF-23, and parathyroid hormone (PTH). LVH independently predicts sudden cardiac death, heart failure, and overall cardiovascular mortality- mechanisms include impaired myocardial relaxation, subendocardial ischemia due to increased oxygen demand, and susceptibility to ventricular arrhythmias.

6.2 Uremic Cardiomyopathy

The uremic milieu is profoundly cardiotoxic. Retained uremic solutes- including indoxyl sulfate, p-cresol sulfate, and ADMA- impair mitochondrial function, promote oxidative stress, and induce apoptosis in cardiomyocytes and vascular endothelial cells. Anemia secondary to reduced erythropoietin (EPO) production imposes a compensatory high-output hemodynamic state that, if sustained, leads to eccentric LVH and, ultimately, dilated cardiomyopathy. Disordered calcium-phosphate metabolism- characterized by hyperphosphatemia, secondary hyperparathyroidism, and elevated FGF-23- promotes myocardial calcification, fibrosis, and diastolic dysfunction.

Uremic pericarditis, though less common in the modern dialysis era, remains a manifestation of severe uremic cardiotoxicity. Its pathogenesis involves direct inflammation of the pericardium by uremic toxins and cytokines including interleukin-1, interleukin-6, and tumor necrosis factor-alpha.

6.3 Arrhythmia and Sudden Cardiac Death

Patients with CKD have a two- to fourfold increased risk of sudden cardiac death (SCD) compared to the general population, reflecting the convergence of multiple arrhythmic substrates: LVH with conduction delays, myocardial fibrosis, electrolyte disturbances (hyperkalemia, hypomagnesemia), autonomic dysfunction with reduced heart rate variability, and calcification of the cardiac conduction system. Hyperkalemia- the most immediately life-threatening electrolyte complication of advanced CKD and ESRD- slows cardiac conduction and can precipitate fatal ventricular arrhythmias.

7. Therapeutic Implications

7.1 RAAS Blockade

ACE inhibitors and angiotensin receptor blockers (ARBs) are the cornerstone of cardiorenal protective therapy. Beyond blood pressure reduction, RAAS blockade reduces intraglomerular hypertension, suppresses aldosterone-mediated fibrosis, and attenuates neurohormonal activation in heart failure. Landmark trials- HOPE, ONTARGET (ACE inhibitors/ARBs), RALES and EMPHASIS-HF (aldosterone antagonists)- established mortality benefits in heart failure with reduced ejection fraction (HFrEF). In proteinuric CKD, RAAS blockade reduces progression to ESRD by approximately 20–30% in landmark trials (IDNT, RENAAL, AASK).

7.2 SGLT2 Inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2i)- originally developed as glucose-lowering agents — have transformed cardiorenal medicine. By inhibiting proximal tubular sodium-glucose reabsorption, SGLT2i induce glycosuria and modest natriuresis, reduce intraglomerular pressure through TGF-mediated afferent arteriolar constriction, and lower blood pressure without activating RAAS. The EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, CREDENCE, DAPA-CKD, and EMPEROR-Reduced trials collectively demonstrated significant reductions in cardiovascular death, hospitalization for heart failure, and CKD progression across diverse cardiometabolic populations, including patients without diabetes. SGLT2i are now recommended by major guidelines for HFrEF and proteinuric CKD regardless of glycemic status.

7.3 Diuretics

Loop diuretics (furosemide, torasemide) inhibiting NKCC2 remain essential for decongestion in acute heart failure and CKD-associated volume overload. Thiazide and thiazide-like diuretics (hydrochlorothiazide, chlorthalidone, indapamide) are effective first-line antihypertensives that act by inhibiting NCC in the distal tubule. Mineralocorticoid receptor antagonists (spironolactone, eplerenone) block aldosterone's fibrotic and sodium-retaining effects, reducing mortality in HFrEF and exhibiting promising renoprotective properties. The novel non-steroidal MRA finerenone has demonstrated

significant cardiorenal benefits in the FIDELIO-DKD and FIGARO-DKD trials.

7.4 Renal Denervation

Catheter-based renal denervation (RDN) uses radiofrequency energy or ultrasound to disrupt renal sympathetic afferent and efferent nerves within the renal artery wall. After early inconclusive results (SYMPLICITY HTN-3), sham-controlled trials employing improved techniques (RADIANCE-HTN TRIO, SPYRAL HTN-ON MED) demonstrated significant blood pressure reductions in resistant hypertension. RDN received regulatory approval in the United States in 2023 and represents an adjunctive option for patients with inadequately controlled hypertension despite optimal pharmacotherapy.

7.5 Erythropoiesis-Stimulating Agents and Iron Therapy

Anemia in CKD, driven primarily by reduced EPO synthesis and iron deficiency, exacerbates cardiac stress through high-output hemodynamics and tissue hypoxia. Erythropoiesis-stimulating agents (ESAs) and intravenous iron correct anemia, reduce transfusion dependence, and improve quality of life. However, targeting hemoglobin levels above 11.5 g/dL with ESAs has been associated with increased stroke and thromboembolic risk in clinical trials (CREATE, CHOIR, TREAT), underscoring the importance of individualized, conservative targets.

8. Emerging Concepts and Future Directions

Several emerging areas promise to expand our mechanistic understanding and therapeutic repertoire. The gut-kidney-heart axis, mediated by trimethylamine N-oxide (TMAO) and other microbiome-derived metabolites, is increasingly recognized as a modifiable cardiovascular risk factor in CKD. Novel biomarkers — including plasma klotho, soluble ST2, galectin-3, and urinary proteomics panels — may enable earlier identification of cardiorenal risk and monitor therapeutic responses. Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), such as roxadustat and daprodustat, represent a new class of anemia therapy that stimulates endogenous EPO production, with potential pleiotropic cardiovascular and renoprotective effects under investigation. Personalized medicine approaches, integrating genomic, metabolomic, and clinical data, aim to tailor RAAS, diuretic, and sympatholytic therapy to individual cardiorenal phenotypes.

The recent FLOW trial demonstrated that the GLP-1 receptor agonist semaglutide significantly reduces CKD progression and cardiovascular events in patients with type 2 diabetes and CKD, adding another dimension to integrated cardiorenal metabolic therapy. The convergence of nephrology, cardiology, and metabolic medicine- now sometimes termed "cardionephrology" or the "cardiometabolic" field- reflects a clinical and scientific paradigm shift toward integrated organ-system medicine.

9. Conclusion

The kidney is a master regulator of the cardiovascular system. Through precise, multilevel control of sodium balance and extracellular fluid volume, RAAS activation, sympathetic modulation, and production of a rich array of vasoactive and trophic hormones, the kidney continuously calibrates blood pressure and preserves cardiac homeostasis. When these mechanisms are disrupted — by intrinsic renal disease, hemodynamic stress, or systemic metabolic disorders- cardiorenal syndrome emerges as a clinically devastating bidirectional feedback loop of organ injury.

Modern medicine has witnessed remarkable therapeutic progress: RAAS inhibitors and SGLT2 inhibitors have reshaped prognosis for millions with heart failure and CKD, while emerging therapies continue to expand the armamentarium. Yet the global burden of hypertension, CKD, and heart failure remains enormous. Deeper mechanistic insight, novel biomarkers, precision therapeutics, and interdisciplinary care models — bridging nephrology, cardiology, and metabolic medicine- will be essential to translate scientific advances into improved patient outcomes worldwide.

Disclosures and Conflicts of Interest
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