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Cardiorenal inflammation in hypertension: Mechanisms of fibrosis and tissue damage

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Abstract
Hypertension is a major driver of cardiovascular and renal injury and is increasingly recognized as a chronic inflammatory disorder rather than solely a hemodynamic disease. Persistent elevation of blood pressure promotes activation of the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, oxidative stress, endothelial dysfunction, immune-cell activation, and maladaptive extracellular-matrix remodeling. These processes interact bidirectionally between the heart and kidneys, creating a self-reinforcing cardiorenal inflammatory–fibrotic cycle. Angiotensin II and aldosterone stimulate reactive oxygen species production, inflammatory signaling, and profibrotic pathways, including transforming growth factor-β (TGF-β)/Smad and connective tissue growth factor pathways. In parallel, activation of macrophages, T cells, monocytes, and inflammasome pathways promotes the release of cytokines such as tumour necrosis factor-α, interleukin-1β, and interleukin-6. Chronic inflammation subsequently activates fibroblasts and myofibroblasts, leading to excessive deposition of extracellular-matrix proteins and progressive fibrosis in the myocardium and kidney. Cardiac fibrosis contributes to ventricular stiffness, hypertrophy, and impaired function, whereas renal glomerular and tubulointerstitial fibrosis progressively reduces filtration capacity. The resulting decline in renal function further aggravates cardiovascular stress through volume overload, neurohormonal activation, and systemic inflammation. Understanding this interconnected inflammation–oxidative stress–fibrosis network provides an important framework for developing therapies aimed not only at lowering blood pressure but also at preventing or reversing target-organ damage.

Keywords: Hypertension, cardiorenal syndrome, inflammation, fibrosis, renin–angiotensin–aldosterone system, oxidative stress, TGF-β, myocardial fibrosis, renal fibrosis, tissue damage

Introduction

Hypertension is one of the most important modifiable risk factors for cardiovascular and kidney disease. Although increased arterial pressure directly exposes the heart, kidneys, and vasculature to mechanical stress, the resulting tissue injury cannot be explained by hemodynamic forces alone. Increasing evidence indicates that hypertension involves sustained activation of innate and adaptive immune responses, oxidative stress, endothelial dysfunction, and inflammatory signaling. Immune cells—including T cells, monocytes, macrophages, dendritic cells, B cells, and natural killer cells—can accumulate in cardiovascular and renal tissues and release inflammatory mediators that promote vascular remodeling, renal injury, cardiac hypertrophy, and fibrosis (Guzik *et al*., 2024; Nguyen *et al*., 2024) [4, 5].

The heart and kidneys are closely interconnected through hemodynamic, neurohormonal, inflammatory, and metabolic pathways. Dysfunction of either organ can initiate compensatory responses that ultimately contribute to injury in the other, producing a bidirectional cardiorenal interaction. Contemporary models of cardiorenal syndrome identify hemodynamic disturbances, activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system, oxidative stress, inflammation, endothelial dysfunction, and progressive tissue fibrosis as interconnected mechanisms underlying cardiorenal injury. In chronic hypertension, persistent activation of these pathways can transform initially compensatory responses into maladaptive processes, promoting structural remodeling and progressive dysfunction of both the heart and kidneys (Dutta *et al*., 2025; Zhao *et al*., 2025) [2, 7].

A central feature of cardiorenal tissue injury is the transition from persistent inflammation to pathological fibrosis. Chronic inflammatory signaling establishes a profibrotic microenvironment characterized by increased cytokines and growth factors, particularly transforming growth factor-β (TGF-β), which promotes fibroblast activation and differentiation into myofibroblasts. Activated myofibroblasts subsequently produce excessive extracellular-matrix (ECM) proteins, including fibrillar collagens, resulting in progressive matrix accumulation, tissue stiffening, disruption of normal architecture, and impaired organ function. In cardiorenal syndrome, this inflammation-to-fibrosis transition involves immune-cell infiltration, macrophage phenotypic changes, TGF-β signaling, myofibroblast activation, and increased deposition of collagen types I, III, IV and other ECM components in the heart and kidneys (Dutta *et al*., 2025; Zhang *et al*., 2025; Cabrera-Fuentes *et al*., 2025) [2, 6].

Hypertension as an Inflammatory Disease

The inflammatory paradigm of hypertension has substantially expanded the understanding of hypertensive target-organ damage. Increased blood pressure, mechanical strain, oxidative stress, high dietary sodium, sympathetic activation, and RAAS stimulation can promote the formation of endogenous danger signals and neoantigens.

These signals activate immune cells and inflammatory pathways, including the NLRP3 inflammasome and nuclear factor-κB (NF-κB). Activated immune cells subsequently migrate into the vasculature, kidneys, and heart and release cytokines and chemokines that reinforce local tissue injury (Guzik *et al*., 2024) [4].

T lymphocytes are particularly important in this response. Effector T-cell populations can release interleukin-17 (IL-17), interferon-γ, and tumour necrosis factor-α (TNF-α), whereas regulatory T cells and anti-inflammatory mediators such as interleukin-10 can exert protective effects. These inflammatory mediators impair nitric-oxide bioavailability, promote vascular contraction, alter renal sodium handling, and stimulate fibrotic pathways.

Thus, hypertension can be viewed as a condition in which hemodynamic stress and immune activation reinforce one another. Vascular inflammation increases vascular stiffness and resistance, while renal inflammation promotes sodium retention and impaired pressure regulation, further sustaining hypertension.

RAAS Activation and Cardiorenal Injury

The RAAS is one of the major molecular systems linking hypertension with cardiac and renal fibrosis. Persistent RAAS activation increases the production of angiotensin II (Ang II) and aldosterone. Through the angiotensin II type-1 receptor (AT1R) and mineralocorticoid receptor, respectively, these mediators promote vasoconstriction, sodium retention, oxidative stress, inflammation, cellular hypertrophy, and extracellular-matrix accumulation (Mennuni *et al*., 2014) [26].

Ang II also stimulates NADPH oxidase activity, increasing the production of reactive oxygen species (ROS). Excess ROS can activate inflammatory signaling and damage cellular proteins, lipids, mitochondria, and DNA. Importantly, oxidative stress and RAAS activation can reinforce each other, creating a positive-feedback loop that sustains tissue injury (Dikalov and Nazarewicz, 2013) [27].

In the kidney, Ang II promotes fibroblast-to-myofibroblast transition and increases the expression of TGF-β and connective tissue growth factor (CTGF), thereby stimulating extracellular-matrix deposition. These processes contribute to glomerulosclerosis and tubulointerstitial fibrosis. In the heart, chronic Ang II signaling promotes cardiomyocyte hypertrophy, fibroblast activation, collagen accumulation, and adverse ventricular remodeling (Delgado-Valero *et al*., 2021) [23].

A protective counter-regulatory RAAS pathway involving ACE2, angiotensin-(1–7), and the Mas receptor opposes many of the effects of the classical ACE/Ang II/AT1R axis. Reduction of this protective pathway can therefore further favor inflammation and fibrosis.

Oxidative Stress as a Link Between Hypertension and Inflammation

Oxidative stress represents a critical intermediate mechanism connecting hypertension to inflammation and fibrosis. Increased Ang II and aldosterone signaling can stimulate NADPH oxidases, particularly NOX2 and NOX4, leading to excessive ROS generation. Recent work on hypertension-associated renal fibrosis describes a mechanistic sequence in which RAAS activation increases ROS, followed by activation of MAPK and NF-κB signaling and subsequent inflammatory and fibrotic responses (Wang *et al*., 2026) [25].

ROS can activate inflammatory transcription factors, promote cytokine production, impair endothelial nitric oxide signaling, and damage mitochondria. Mitochondrial dysfunction may further increase ROS production, creating another self-amplifying cycle. Oxidative stress can also interact with inflammasome signaling and forms part of the molecular environment that promotes cell injury and fibrosis (Checa and Aran, 2020) [24].

In the heart, oxidative stress contributes to cardiomyocyte dysfunction and fibroblast activation. In the kidney, it promotes endothelial injury, tubular damage, glomerular dysfunction, and interstitial inflammation. Therefore, oxidative stress is not merely a consequence of hypertension but an active mediator of progressive cardiorenal damage (Rubattu *et al*., 2013) [22].

Immune Cells and Cytokine-Mediated Tissue Damage

Chronic inflammation in hypertension involves coordinated interactions among immune cells, vascular cells, epithelial cells, fibroblasts, and cardiomyocytes. Monocytes and macrophages are particularly important because they infiltrate injured tissues and can participate in both inflammatory and reparative responses. In cardiorenal fibrosis, macrophage accumulation has been associated with myocardial and renal remodeling, and macrophage phenotypic transitions appear to contribute to the inflammatory-to-fibrotic switch (Cicalese *et al*., 2021) [21].

TNF-α, IL-1β, and IL-6 are among the important cytokines involved in this process. TNF-α can activate NF-κB and contribute to inflammatory and profibrotic signaling. IL-1β has direct profibrotic effects and can stimulate myofibroblast activation through TGF-β-dependent mechanisms. IL-6 can further promote fibroblast activation and extracellular-matrix production (Das and Medhi, 2023) [18].

The NLRP3 inflammasome provides another important connection between hypertension, oxidative stress, inflammation, and tissue injury. Its activation promotes maturation and release of IL-1β and IL-18, thereby sustaining inflammatory signaling. The broader inflammatory response in hypertension can subsequently affect sodium handling, vascular function, cardiac remodeling, and renal fibrosis (Chen *et al*., 2023) [18].

TGF-β and the Inflammation-to-Fibrosis Transition

Among the profibrotic pathways involved in cardiorenal injury, TGF-β is one of the most important. Inflammatory mediators and Ang II can increase TGF-β expression, while TGF-β activates fibroblasts and promotes their differentiation into myofibroblasts (Antar *et al*., 2023) [20].

TGF-β acts through canonical Smad-dependent signaling and several non-canonical pathways. Activation of Smad2/3 promotes transcription of genes involved in extracellular-matrix production, including collagen and other matrix proteins. Consequently, persistent TGF-β signaling results in excessive and poorly degradable extracellular-matrix accumulation (Meng *et al*., 2016) [19].

This pathway is particularly important because it provides a mechanistic explanation for how an initially inflammatory injury becomes a chronic structural abnormality. Once substantial fibrosis develops, the resulting tissue stiffness

and altered architecture can itself promote further dysfunction, establishing a self-sustaining cycle.

Cardiac Fibrosis in Hypertension

Chronic hypertension increases cardiac afterload and stimulates compensatory left ventricular hypertrophy. Initially, hypertrophy may help maintain cardiac function, but persistent pressure overload promotes maladaptive remodeling. Angiotensin II (Ang II), aldosterone, reactive oxygen species (ROS), inflammatory cytokines, and transforming growth factor-beta (TGF-β) stimulate cardiac fibroblasts and promote extracellular-matrix deposition (Díez, 2007; Gekle *et al*., 2006 [15]; Roubille *et al*., 2024).

The accumulation of collagen and other matrix proteins increases myocardial stiffness and disrupts normal ventricular relaxation. Progressive fibrosis can therefore contribute to diastolic dysfunction, atrial enlargement, arrhythmias, and eventually heart failure (Díez, 2007; Røe *et al*., 2017). Inflammatory and fibrotic signaling also interacts with cardiomyocyte hypertrophy and microvascular dysfunction, producing a complex remodeling phenotype.

Current evidence emphasizes the importance of immune-cell and fibroblast interactions in cardiovascular fibrosis. Macrophages, neutrophils, fibroblasts, and myofibroblasts participate in a dynamic inflammatory–fibrotic network that can ultimately produce myocardial stiffening and adverse cardiac remodeling (Hara & Tallquist, 2023) [16].

Renal Fibrosis in Hypertension

The kidney is both a target and a driver of hypertension. Chronic pressure elevation causes glomerular hypertension, endothelial dysfunction, vascular injury, tubular stress, and activation of inflammatory and fibrotic pathways. Ang II, aldosterone, ROS, inflammatory cytokines, and TGF-β collectively promote glomerulosclerosis and tubulointerstitial fibrosis (Díez, 2007).

Tubular epithelial injury is particularly important because persistent injury stimulates inflammatory-cell recruitment and fibroblast activation in the renal interstitium. Progressive deposition of extracellular matrix disrupts the normal relationship between tubules, capillaries, and interstitial cells, ultimately reducing functional nephron mass.

Recent mechanistic work identifies a RAAS–ROS–inflammation–fibrosis axis as a central pathway in hypertension-associated renal fibrosis. In this model, RAAS activation increases ROS production, ROS activates inflammatory pathways, and inflammation subsequently stimulates TGF-β, PDGF, lysophosphatidic-acid signaling, and other profibrotic pathways.

The Bidirectional Cardiorenal Fibrotic Cycle

Cardiac and renal fibrosis should not be considered independent processes. Instead, they form part of a dynamic cardiorenal network.

Hypertension → RAAS/SNS activation → oxidative stress → inflammation → fibrosis → organ dysfunction → further cardiorenal stress

For example, cardiac dysfunction can reduce effective renal perfusion and increase venous congestion, promoting renal dysfunction. Declining renal function can then cause sodium and water retention, neurohormonal activation, systemic inflammation, and additional cardiovascular stress. This creates a vicious cycle in which cardiac and renal dysfunction progressively reinforce each other.

Conversely, renal injury can increase circulating inflammatory mediators and uremic factors that adversely affect the myocardium and vasculature. Consequently, the progression of renal fibrosis can accelerate cardiovascular remodeling, while cardiac fibrosis and dysfunction can worsen renal injury (Mezzano *et al*., 2001; Ruiz-Ortega *et al*., 2001) [11].

Other Profibrotic Pathways

Although TGF-β is a central pathway, cardiorenal fibrosis involves multiple interacting mechanisms. Wnt/β-catenin signaling, CTGF, PDGF, endothelin-1, hypoxia-related pathways, mitochondrial dysfunction, endoplasmic-reticulum stress, and non-coding RNAs can contribute to fibroblast activation and matrix accumulation.

The FGF23–Klotho axis is another important component of cardiorenal communication. Renal dysfunction can reduce Klotho availability and increase FGF23, while disturbances in this axis may promote cardiovascular and renal remodeling. Recent evidence suggests that FGF23/Klotho signaling interacts with Wnt and TGF-β pathways during cardiorenal fibrosis.

Galectin-3 is also of interest as both a mediator and biomarker of cardiorenal fibrosis. Produced largely by inflammatory cells, galectin-3 has been associated with macrophage responses and fibrotic remodeling in both cardiac and renal tissues.

Extracellular-Matrix Remodeling and Tissue Damage

Fibrosis represents more than simply an increase in collagen concentration. It involves a fundamental alteration of extracellular-matrix composition, organization, turnover, and mechanical properties. In cardiorenal fibrosis, active myofibroblasts produce excessive amounts of fibrillar collagens, particularly collagen I and III, together with other matrix components.

Excessive matrix deposition reduces tissue compliance and interferes with normal cellular communication. In the heart, this contributes to myocardial stiffness and impaired relaxation. In the kidney, matrix accumulation disrupts glomerular and tubular architecture and reduces filtration capacity.

Matrix metalloproteinases and their inhibitors also become dysregulated during chronic injury. Thus, fibrosis reflects an imbalance between matrix synthesis and degradation rather than increased synthesis alone (Røe *et al*., 2017) [17].

Therapeutic Implications

The mechanisms described above indicate that effective management of hypertensive cardiorenal injury requires more than blood-pressure reduction alone. RAAS blockade remains an important therapeutic strategy because it reduces Ang II/AT1R-mediated hemodynamic, inflammatory, and profibrotic signaling, including pathways that promote TGF-β expression and extracellular-matrix accumulation (Mezzano *et al*., 2001; Ruiz-Ortega *et al*., 2001) [11]. Other established therapies can also influence pathways involved in cardiorenal remodeling.

Recent research has highlighted the potential importance of therapies that simultaneously influence hemodynamic stress,

inflammation, oxidative stress, and fibrosis. SGLT2 inhibitors, for example, have demonstrated important cardiorenal protective effects, while experimental and translational studies suggest that their benefits may involve attenuation of oxidative stress and inflammation and modulation of profibrotic pathways, including TGF-β/Smad signaling (Wang *et al*., 2023; Karakasis *et al*., 2025) [10, 13].

However, directly targeting TGF-β illustrates the difficulty of antifibrotic therapy. Although TGF-β is a major mediator of fibrosis and inhibition of its signaling can be beneficial in experimental models, clinical translation has been challenging because TGF-β also has important physiological roles in immune regulation, tissue homeostasis, and repair (Frangogiannis, 2020; Distler *et al*., 2017) [8, 9].

Future approaches may therefore need to target several interconnected pathways simultaneously—for example, RAAS/oxidative stress, inflammatory signaling, immune-cell activation, fibroblast differentiation, and extracellular-matrix remodeling.

Biomarkers and Future Directions

Improved identification of patients at risk of progressive cardiorenal fibrosis is an important research priority. Potential biomarkers include TGF-β, galectin-3, procollagen peptides, inflammatory cytokines, and markers of renal and cardiac injury. Recent work has associated circulating TGF-β, procollagen peptides, and galectin-3 with cardiorenal fibrosis (Guzik *et al*., 2024) [4].

Nevertheless, translating mechanistic findings into clinical practice remains challenging. Many antifibrotic mechanisms have been demonstrated primarily in experimental models, and their relevance to heterogeneous human disease requires further validation. Better molecular phenotyping, non-invasive assessment of fibrosis, and combination therapeutic strategies may improve the ability to identify and treat patients before irreversible tissue damage develops (Dutta *et al*., 2025) [2].

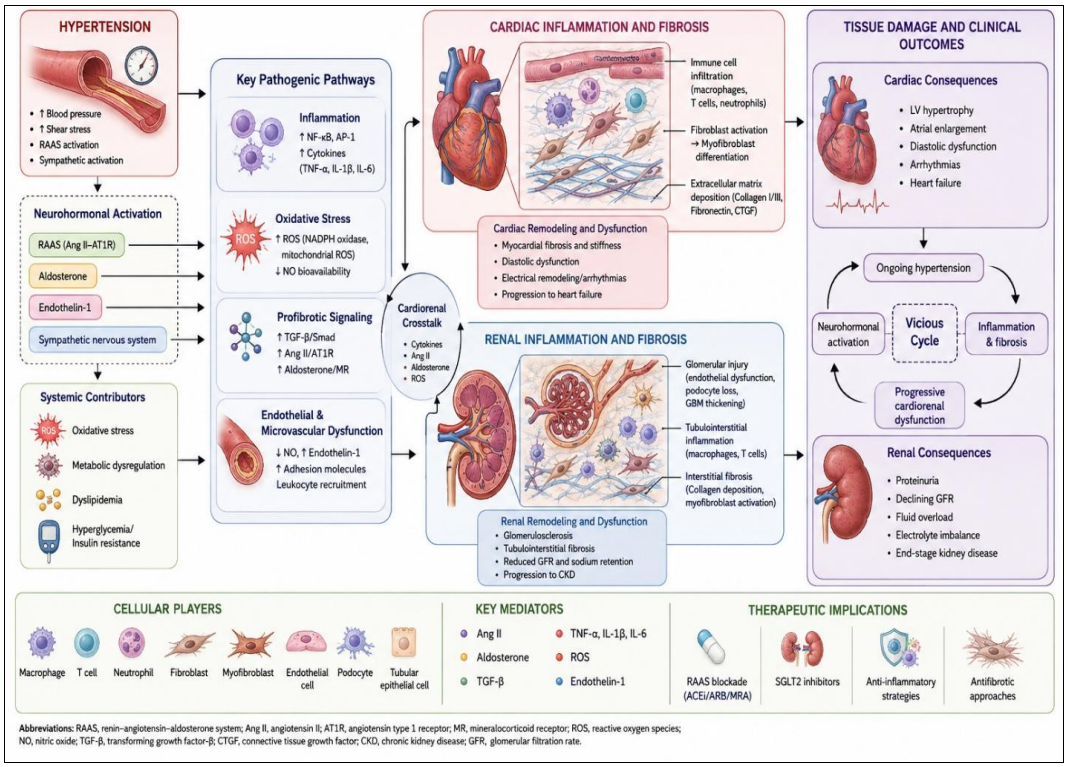

Fig 1: Cardiorenal Inflammation in Hypertension: Mechanisms of Fibrosis and Tissue Damage

Conclusion

Cardiorenal inflammation in hypertension represents a complex interaction between hemodynamic stress, RAAS activation, sympathetic stimulation, oxidative stress, immune-cell activation, endothelial dysfunction, and profibrotic signaling. Rather than acting independently, these pathways form interconnected feedback loops that progressively damage the heart and kidneys. Ang II and aldosterone promote ROS generation and inflammatory signaling, while cytokines such as TNF-α, IL-1β, and IL-6 create a tissue environment that activates fibroblasts and myofibroblasts. TGF-β/Smad signaling then drives excessive extracellular-matrix deposition and the development of cardiac and renal fibrosis. The resulting structural damage further impairs cardiac and renal function, reinforcing the cardiorenal cycle. Current evidence therefore supports a therapeutic paradigm that combines effective blood-pressure control with strategies aimed at interrupting inflammation, oxidative stress, and fibrosis. A deeper understanding of these interconnected mechanisms may enable earlier identification of tissue injury and development of more precise interventions to prevent irreversible cardiorenal remodeling

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