Scientific Research Publishing

Journal of Biosciences and Medicines, 2026, 14(9), 453-472
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

The Spontaneously Hypertensive Rat in the Era of Cardiometabolic Hypertension: Strengths, Limitations and Translational Perspectives

María Fernanda Iñigo-Pío[1], Itzell Alejandrina Gallardo-Ortíz[2], Rafael Villalobos-Molina[2], Santiago Cristóbal Sigrist-Flores[1,2]

[1]Carrera de Médico Cirujano, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Tlalnepantla de Baz, Mexico
[2]Laboratorio 7, Unidad de Biomedicina, División de Investigación y Posgrado, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Tlalnepantla de Baz, Mexico
Email: santiago_sigrist@iztacala.unam.mx

How to cite this paper: Iñigo-Pío, M.F., Gallardo-Ortíz, I.A., Villalobos-Molina, R. and Sigrist-Flores, S.C. (2026) The Spontaneously Hypertensive Rat in the Era of Cardiometabolic Hypertension: Strengths, Limitations and Translational Perspectives. *Journal of Biosciences and Medicines*, **14**, 453-472.
https://doi.org/10.4236/jbm.2026.149028

Received: August 15, 2026
Accepted: September 20, 2026
Published: September 23, 2026

Abstract

The spontaneously hypertensive rat (SHR) remains a cornerstone model for studying essential hypertension and cardiorenal damage. However, its translational relevance must be interpreted within a clinical context in which hypertension frequently coexists with metabolic abnormalities, including obesity, dyslipidemia, insulin resistance, and impaired glucose regulation, features that the lean, largely normoglycemic SHR does not fully reproduce. This review critically re-evaluates the strengths, methodological limitations, and translational utility of the SHR model in the current era of cardiometabolic hypertension. We highlight that cardiorenal injury in the SHR involves mechanisms that extend beyond pressure overload, including tissue renin-angiotensin-aldosterone system (RAAS) dysregulation, mitochondrial remodeling, and sterile inflammation. Furthermore, we propose that, rather than representing a classic low-output cardiorenal syndrome, the SHR may be better viewed as a model of parallel, progressive cardiac and renal injury driven primarily by pressure overload and neurohormonal mechanisms; a contribution of altered venous hemodynamics remains plausible but unproven. Altered venous capacitance and filling pressures suggest a potential contribution of venous hemodynamics to cardiorenal cross-talk, although renal venous hypertension and chronic renal congestion remain unproven in SHR. Despite these mechanistic insights, significant translational barriers persist, notably the "metabolic gap", the phenotypic and genetic variability of SHR/Wistar-Kyoto (WKY) substrains, and the confounding impact of environmental variables such as the gut microbiome. To

bridge these gaps, future research should integrate high-resolution phenotyping, including single-cell and spatial transcriptomics, proteomics, metabolomics, and targeted interrogation of emerging pathways, to define cell-specific pathogenic mechanisms. Ultimately, the SHR should be recognized not as a universal surrogate for human hypertension, but as a precision mechanistic model whose value depends on the biological question under investigation.

Keywords

Spontaneously Hypertensive Rat, Cardiorenal Injury, Cardiometabolic Hypertension, Translational Research, Metabolic Syndrome, Animal Models

1. Introduction

Translational research in arterial hypertension and cardiorenal syndrome continues to face considerable challenges, regarding the predictive capability of experimental models to reproduce the complexity of human disease. Despite the development of multiple surgical, pharmacological, and diet-induced models, the spontaneously hypertensive rat (SHR), developed more than six decades ago, remains one of the most extensively referenced models for studying the mechanisms of primary hypertension and target organ damage [1] [2]. Its continued relevance is due not merely to a consequence of historical precedent, but also to the key conceptual advantage: SHR allows to study the interaction between genetic, hemodynamic, and neurohormonal determinants involved in primary hypertension, without the influence of secondary factors introduced by experimentally induced models (*i.e.*, high salt ingestion), or associated comorbidities. In SHR, the progressive increase in blood pressure and the subsequent cardiovascular and renal remodeling emerge spontaneously, reproducing key components of the progression of human hypertension [3].

However, this mechanistic simplification represents a limitation for translational interpretation. In human populations, hypertension frequently coexists with individual metabolic abnormalities, including obesity, dyslipidemia, insulin resistance, and impaired glucose regulation, while a subset of hypertensive patients fulfills formal diagnostic criteria for metabolic syndrome [4] [5]. These metabolic abnormalities may modify the pathophysiological context of hypertension through additional inflammatory, neurohormonal, and metabolic mechanisms [6] [7]. In contrast, the SHR predominantly exhibits a lean phenotype and remains largely normoglycemic during much of its lifespan [2]. This phenotypic discrepancy generates a scientific paradox: the model permits precise dissection of mechanisms related to pressure overload and neurohormonal activation, but it does not reproduce the metabolic complexity present in many hypertensive clinical populations (**Figure 1**). The aim of this work is to critically analyze the strengths, limitations, and utility of the SHR as a model of cardiorenal investigation, rather than to provide an exhaustive description of the SHR phenotype.

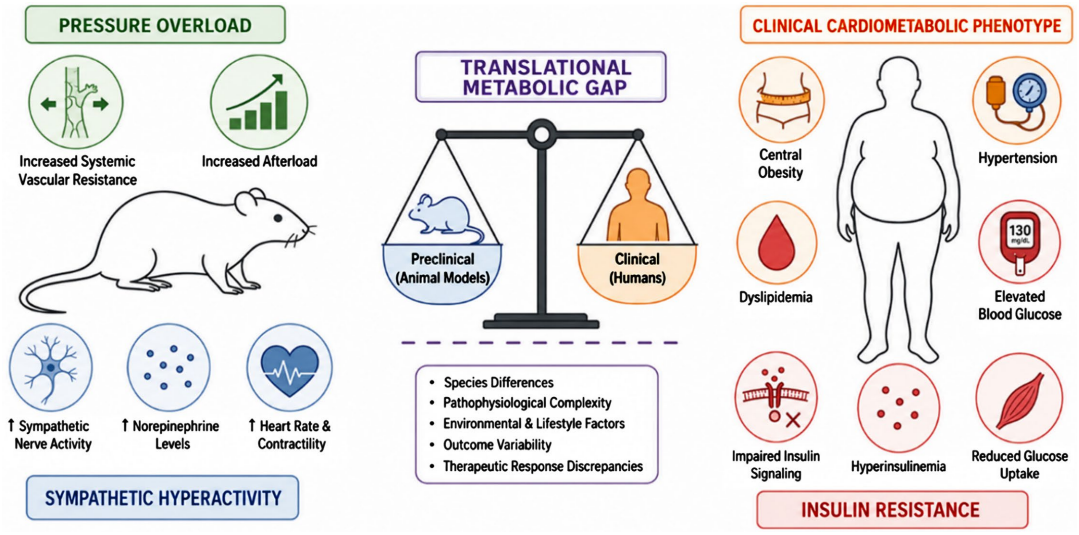

Figure 1. The SHR Paradox in the Era of Cardiometabolic Hypertension. The spontaneously hypertensive rat (SHR) excels at dissecting mechanisms of pressure overload and neurohormonal activation (Left Panel). However, its lean and largely normoglycemic phenotype contrasts with hypertensive populations in which obesity, dyslipidemia, insulin resistance, impaired glucose regulation, or formal metabolic syndrome frequently coexist (Right Panel). This phenotypic discrepancy creates a translational metabolic gap that must be considered when extrapolating findings (Center). Source: Elaborated with https://www.lovart.ai.

The central questions are: what cardiorenal pathophysiological mechanisms can be inferred from the SHR model? And to what extent does the absence of metabolic alterations affect the translational interpretation of these findings? To approach these questions is useful to consider the damage to the target organ, as a process that goes beyond the isolated effect of blood pressure, and incorporates the transition from initial adaptive responses through maladaptive status, mediated by molecular network responses.

2. Characterizing the SHR Model

From the Hypertensive Phenotype to Cardiorenal Adaptation

The spontaneously hypertensive rat (SHR) phenotype is not only defined by the increase in systemic blood pressure, but also by a substantial reprogramming of the cardiovascular and renal control systems. One of the earliest pathophysiological events in this model is sympathetic hyperactivity, a key component. This alteration appears before the established hypertension is manifested, which has led to the proposal that it actively participates at the beginning of the hypertensive phenotype, and not only represents a secondary response to the hemodynamic alterations associated to the disease [8].

Increased sympathetic tone not only augments ventricular afterload, but also directly affects the kidneys through renal sympathetic nerve activity, thereby modifying pressure-natriuresis and favoring sodium retention [6] [8]. This sympathetic activation intersects with the renin-angiotensin-aldosterone system (RAAS); however, SHR studies indicate that circulating and tissue RAAS components

should not be considered equivalent. Plasma renin activity may be normal or reduced after hypertension is established, whereas renal and extra-renal RAAS components show age- and tissue-dependent regulation [9] [10]. Thus, rather than a uniform systemic RAAS activation, the SHR displays a compartmentalized and stage-dependent RAAS phenotype.

SHR-specific studies support tissue-specific RAAS regulation. In the heart, ACE inhibition reduced left ventricular hypertrophy together with cardiac tissue angiotensin II content, despite the absence of parallel reductions in circulating angiotensin II [11]. In the kidney, angiotensin II and its response to ACE inhibition differ between renal tissue and plasma, supporting partial independence of tissue and circulating RAAS [10]. Therefore, rather than assuming uniformly increased local angiotensin II signaling across organs and ages, the available evidence supports dysregulated, tissue- and stage-dependent RAAS signaling that may contribute to cardiac, vascular, and renal remodeling.

Facing this sustained neurohormonal and hemodynamic load, the heart and the kidneys deploy initial adaptive responses. The myocardium develops concentric left ventricular hypertrophy, a mechanism intended to normalize the wall stress due to the afterload increase [12]. Facing this sustained neurohormonal and hemodynamic load, the heart and kidneys exhibit age-dependent responses. The myocardium develops concentric left ventricular hypertrophy, an initially compensatory mechanism that reduces wall stress in response to increased afterload [12]. In contrast, young adult SHR generally maintain relatively preserved renal function and exhibit limited hypertensive renal injury despite elevated systemic blood pressure. With aging, glomerular capillary pressure increases and precedes proteinuria and structural injury, after which progressive glomerulosclerosis and tubulointerstitial damage may emerge [13]. Thus, renal injury in the SHR should be interpreted as an age- and context-dependent process rather than as an inevitable early consequence of hypertension. The relative contribution of these mechanisms changes along the model evolution: in the pre-hypertensive steps the compensatory responses predominate, while in the established hypertension there is a progressive increase in the influence of maladaptive mechanisms.

As hemodynamic and neurohormonal stress persists, initially adaptive responses may progressively become maladaptive and become associated with structural remodeling, functional impairment, and target-organ injury. In SHR, RAAS/AT1R-related signaling has been associated with oxidative stress and inflammatory pathways. ACE inhibition reduces cardiac tissue angiotensin II and left ventricular hypertrophy and modifies renal tissue angiotensin profile [10] [11]. whereas selective α_{1D}-adrenoceptor blockade with BMY 7378 reverses established cardiac hypertrophy [14]. These findings support contri an association between neurohormonal pathways to target-organ remodeling but do not establish a single causal sequence across organs and disease stages. Podocyte injury and associated filtration-barrier alterations, endothelial dysfunction, and progressive fibrosis have also been reported in SHR [15].

3. Cardiorenal Network in SHR

Integrating the Oxidative Stress, Inflammation and Fibrosis

Progression from early hemodynamic adaptation to structural injury in SHR does not follow a single predictable linear sequence. Instead, available evidence supports an interacting network in which mechanical overload, tissue-specific RAAS dysregulation, mitochondrial remodeling, oxidative stress, inflammation, and fibrosis coexist and may reinforce one another (**Figure 2**). Although experimental studies support links among these processes, their temporal and causal hierarchy has not been established uniformly across organs, ages, or SHR substrains. Accordingly, this framework is best interpreted as a network of associated and potentially reciprocal mechanisms rather than as a fixed causal cascade.

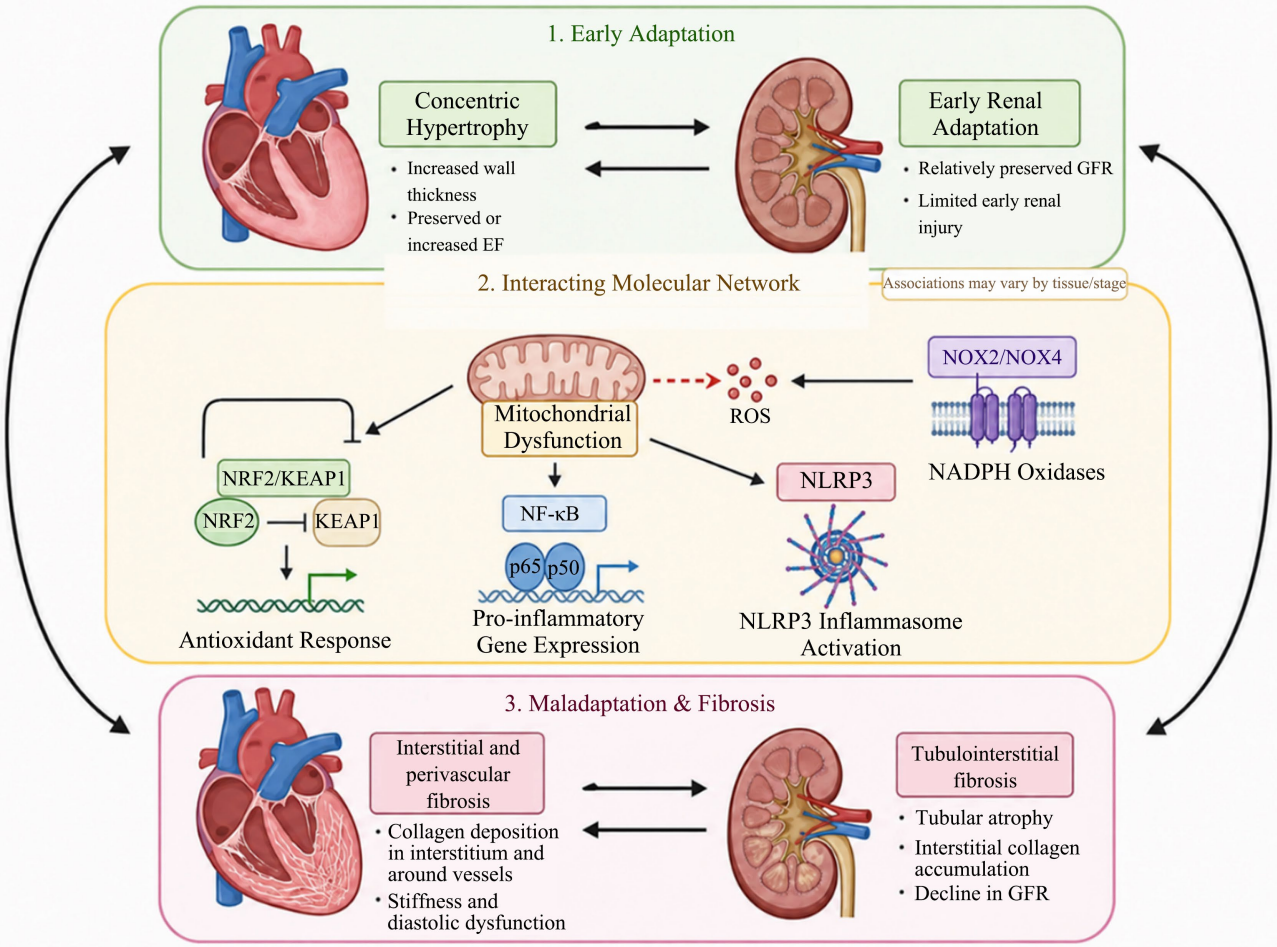

Figure 2. The Cardiorenal Network in SHR: Integration of Oxidative Stress, Inflammation, and Fibrosis. The progression from adaptive to maladaptive cardiorenal injury in SHR is represented as an interacting, non-linear network rather than a fixed causal cascade. Phase 1 (Early Adaptation): sympathetic hyperactivity and tissue-specific RAAS dysregulation are associated with concentric hypertrophy and glomerular hyperfiltration. Phase 2 (Interacting Molecular Network): mitochondrial remodeling, NADPH oxidases, oxidative stress, NRF2/KEAP1, NF-κB, and NLRP3 are interconnected, with directionality varying by tissue and disease stage. Phase 3 (Maladaptation): persistent inflammatory and profibrotic signaling is associated with cardiac and renal fibrosis. A direct role for chronic renal venous congestion as a spontaneous driver of SHR renal injury remains unproven. Source: Elaborated with https://www.lovart.ai.

The intersection of hemodynamic load and angiotensin/AT1R signaling has been associated with NADPH oxidase-derived ROS in hypertension [16] [17]; however, SHR-specific mitochondrial findings are heterogeneous and depend on organ, age, and disease stage. In compensatorily hypertrophied SHR myocardium, mitochondrial complex I/II activity and SirT1/AMPK-PGC-1alpha signaling were reduced and Drp1/OPA1 remodeling was altered [18]. A separate SHR study reported reduced baseline MFN2 and OPA1 expression in the heart, and an impaired mitochondrial adaptive response to exercise [19]. Conversely, kidneys of young prehypertensive SHR can exhibit increased PGC-1alpha, mitochondrial transcription factors, and OXPHOS proteins, suggesting an early compensatory response to increased energetic demand [20], whereas established hypertension has been associated with impaired renal mitochondrial oxidative phosphorylation [21]. Therefore, mitochondrial alterations in SHR should not be interpreted as a uniform downstream consequence of NOX-derived ROS; rather, they appear to represent tissue- and stage-dependent remodeling that may interact bidirectionally with redox imbalance.

NRF2/KEAP1 constitutes a central antioxidant regulatory system. In SHR, renal NRF2-related defenses are altered, but their direction and magnitude depend on age, tissue, and intervention. Javkhedkar *et al.* reported impaired renal Nrf2 signaling and reduced downstream antioxidant defenses in SHR, whereas resveratrol restored Nrf2 activity and attenuated renal oxidative and inflammatory injury [22]. More recently, celastrol treatment in SHR was associated with activation of the Nrf2/HO-1 pathway, reduction of oxidative stress, and improvement of renal injury [23]. These intervention studies support a role for NRF2-related antioxidant defenses in SHR renal injury; however, they do not establish a universal progressive "exhaustion" of antioxidant capacity throughout the lifespan.

The resulting redox imbalance may favor persistent inflammatory responses. NF-κB activation and inflammatory cytokines have been associated with hypertensive tissue injury [24] [25]. Importantly, NLRP3 inflammasome activation has been demonstrated directly in SHR kidney: Chen *et al.* reported increased renal cortical NLRP3 activity and mature IL-1β, whereas BCL6 overexpression reduced NLRP3 expression, renal inflammation, and blood pressure [26]. NLRP3-related signaling has also been implicated in cardiac remodeling in SHR intervention studies [27]. These findings support an association between inflammasome activity and hypertensive tissue injury in SHR; however, the sequence linking mitochondrial ROS, NLRP3 activation, immune-cell recruitment, and subsequent fibrosis should not be presented as uniformly causal without longitudinal or intervention evidence for each step.

TGF-β/SMAD signaling is a well-established profibrotic pathway [28] [29]. In SHR, cardiac and renal fibrosis coexist with oxidative and inflammatory abnormalities, and interventions targeting neurohormonal, inflammatory, or redox pathways can attenuate fibrotic and injury markers [15] [30]. These data are consistent with cross-regulation among oxidative, inflammatory, and profibrotic

pathways, but ROS and cytokines should be regarded as potential contributors, rather than as components of an obligatory linear sequence. In the heart, interstitial and perivascular fibrosis are associated with myocardial stiffening and impaired relaxation, whereas renal tubulointerstitial fibrosis is associated with microvascular rarefaction and hypoxic stress. The coexistence of cardiac and renal remodeling provides a biological basis for parallel organ injury; however, it does not by itself demonstrate direct bidirectional heart-kidney signaling.

Renal interstitial fibrosis and tubular hypoxia may stimulate local profibrotic and vasoactive mediators, including endothelin-1 and TGF-β, and may therefore participate in systemic humoral and neurohormonal interactions [31] [32]. SHR-specific evidence also demonstrates abnormalities of the venous circulation. Emans *et al.* reported increased mean circulatory filling pressure, enhanced sympathetic venoconstrictor activity, and reduced mesenteric venous capacitance in conscious hypertensive rats [33]. Longitudinal studies in SHR have also identified an age-dependent stage characterized by increased left ventricular end-diastolic pressure, while ejection fraction remains preserved [34]. Together, these findings provide a physiological basis for considering altered venous hemodynamics as a potential contributor to cardiorenal interaction. However, sustained renal venous hypertension and chronic renal congestion have not been directly demonstrated as spontaneous drivers of renal injury in untreated SHR.

4. From the Classic Cardiorenal Syndrome to Parallel Cardiorenal Injury in the SHR: Potential Contribution of Altered Venous Hemodynamics

The integration of neurohormonal, redox, inflammatory, and fibrotic abnormalities prompts reconsideration of how cardiorenal injury should be interpreted in SHR. In clinical settings, type 1 cardiorenal syndrome is characterized by an acute worsening of cardiac function that promotes acute kidney injury. Its pathophysiology is multifactorial and may involve impaired forward flow, elevated venous pressures, neurohormonal activation, endothelial dysfunction, and inflammation [31] [32]. This acute clinical syndrome does not reproduce the gradual natural history of untreated SHR, in which cardiac and renal abnormalities develop progressively under sustained hypertension and shared neurohormonal stress. Recent SHR studies document concurrent cardiac and renal injury and fibrosis [30]. Moreover, experimentally superimposed myocardial infarction-induced heart failure in SHR aggravates renal injury, demonstrating that cardiorenal interaction can occur in this model under additional cardiac stress [35]. However, that induced model should not be taken as evidence that the same heart-to-kidney pathway is the dominant mechanism in untreated SHR. Moreover, experimentally superimposed myocardial infarction-induced heart failure in SHR aggravates renal injury, demonstrating that cardiorenal interaction can occur in this model under additional cardiac stress [35]. However, that induced model should not be taken as evidence that the same heart-to-kidney pathway is the dominant mechanism in untreated SHR.

During aging, SHR develop progressive left ventricular hypertrophy, fibrosis, and abnormalities of diastolic function. In a longitudinal study, Fu *et al.* identified a stage in which left ventricular end-diastolic pressure was elevated while ejection fraction remained preserved, preceding overt systolic dysfunction [34]. SHR-specific studies also demonstrate altered systemic venous physiology; Emans *et al.* reported increased mean circulatory filling pressure and reduced mesenteric venous capacitance associated with enhanced sympathetic venoconstrictor activity [33]. These observations establish abnormalities of cardiac filling pressure and venous capacitance in spontaneous hypertension, but they do not directly demonstrate sustained elevation of renal venous pressure. Evidence from heart-failure studies ans experimental models outside the untreated SHR indicates that increased renal venous pressure can reduce renal plasma flow and glomerular filtration rate [32] [36]; therefore, extrapolation of this pathway to spontaneous SHR cardiorenal injury should remain explicitly hypothetical.

Simultaneously, SHR kidneys develop injury through mechanisms directly documented in the model, including intraglomerular hypertension, altered renal vascular resistance, tissue-specific RAAS signaling, oxidative stress, inflammation, and progressive fibrosis. Thus, cardiac and renal injury in SHR need not be interpreted as a unidirectional sequence; both organs undergo progressive remodeling under shared hemodynamic and neurohormonal stressors. The combination of increased cardiac filling pressures and altered systemic venous capacitance, raises the possibility that backward venous pressure transmission could additionally influence renal hemodynamics, but this has not been directly established in untreated SHR. Longitudinal studies simultaneously measuring cardiac filling pressures, central and renal venous pressures, renal perfusion, and structural markers of renal congestion will be required to test this hypothesis. From this perspective, the SHR is best viewed as a model of parallel and progressive cardiorenal injury in which a contribution of altered venous hemodynamics remains plausible but unproven (**Figure 3**).

5. Biological and Methodological Limitations of the SHR Model

The utility of the SHR model for cardiorenal research must be interpreted within its biological and methodological limits. The model enables detailed analysis of hemodynamic and neurohormonal mechanisms, but its predictive value depends on both phenotypic differences from human disease and experimental implementation [2]. These limitations can be divided into external-validity challenges, related to the clinical contexts that the model does or does not reproduce, and internal-validity challenges, related to standardization and experimental control. Importantly, the timing and magnitude of blood-pressure elevation, metabolic phenotype, and target-organ injury in SHR vary with substrain and colony source, sex, diet, housing conditions, and the method used to measure blood pressure; these variables should therefore be considered part of the phenotype rather than incidental methodological details [2] [37] [38].

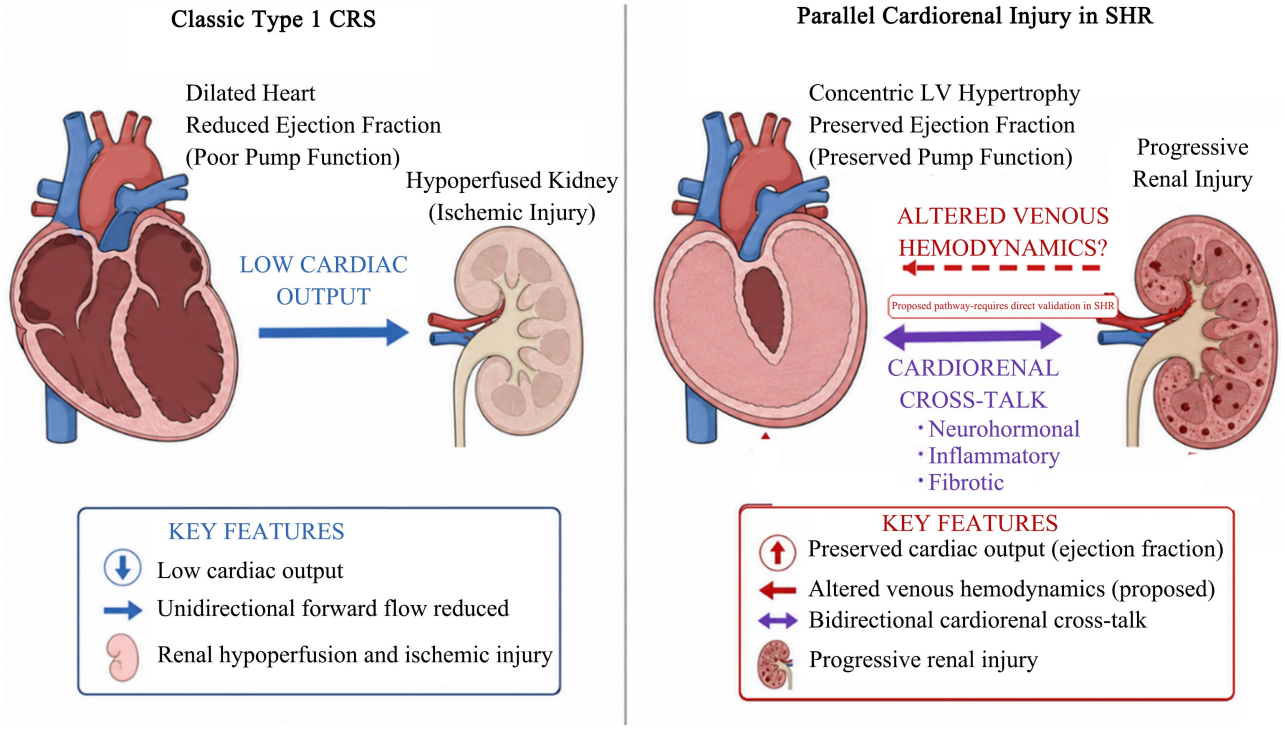

Figure 3. Reconceptualizing Cardiorenal Injury in SHR: Established Features and a Proposed Venous-Hemodynamic Pathway. Panel A: Classic Type 1 cardiorenal syndrome involves an acute cardiac event with reduced cardiac output and renal hypoperfusion. Panel B: In SHR, cardiac and renal remodeling develop progressively under sustained hypertension and neurohormonal stress. SHR-specific studies demonstrate left ventricular hypertrophy, age-dependent elevations in filling pressure, and altered systemic venous capacitance. These findings raise the hypothesis that altered venous hemodynamics may contribute to heart-kidney cross-talk; however, sustained renal venous hypertension and chronic renal congestion have not been directly demonstrated as spontaneous drivers of renal injury in untreated SHR. The venous pathway shown is therefore a testable hypothesis rather than an established characteristic of the model. Source: Elaborated with https://www.lovart.ai.

5.1. The Metabolic Gap

In clinical practice, hypertension frequently coexists with metabolic abnormalities, such as central obesity, dyslipidemia, insulin resistance, and impaired glucose regulation. Importantly, the presence of one or more of these abnormalities should be distinguished from the formal diagnosis of metabolic syndrome, which requires a defined combination of metabolic risk factors. The prevalence of metabolic syndrome among individuals with hypertension varies with population characteristics, diagnostic criteria, age, and hypertension severity. In the GOOD observational survey, which included 3370 adult hypertensive outpatients from 305 sites across 12 European countries, approximately 58% fulfilled criteria for metabolic syndrome [4]. In a separate Brazilian cohort of 236 hypertensive patients, metabolic syndrome was reported in 66% overall, including 73% of patients with resistant hypertension and 60% of those with mild-to-moderate hypertension [5]. These findings demonstrate that metabolic syndrome and its individual components are highly prevalent in selected hypertensive populations, but they should not be interpreted as evidence that all, or necessarily most, individuals with hypertension have a uniform cardiometabolic phenotype. The coexistence of met-

abolic abnormalities is pathophysiologically relevant because obesity, insulin resistance, dyslipidemia, and related disturbances can introduce additional inflammatory, neurohormonal, and metabolic mechanisms [6] [7]. In contrast, the classic SHR predominantly exhibits a lean phenotype and remains largely normoglycemic during much of its lifespan [2]. Therefore, the principal translational limitation is not failure to reproduce a universal hypertensive phenotype, but failure to incorporate the metabolic comorbidities present in important subsets of patients with hypertension.

Therapeutic responses observed in SHR should therefore be extrapolated cautiously to metabolically complex settings. Interventions that modify oxidative stress or neurohormonal pathways in the lean SHR may behave differently in models in which obesity, insulin resistance, dyslipidemia, inflammation, and lipotoxicity coexist [7] [12]. The SHR is consequently best regarded as a mechanistic model of genetic hypertension, rather than as a comprehensive representation of the full phenotypic heterogeneity of contemporary hypertensive populations [2] [39]-[42].

5.2. Internal Validation and Reproducibility: Challenges Related to Controls and Environmental Factors

WKY rats have historically been used as the normotensive reference strain for SHR because of their shared Wistar ancestry; however, substantial genetic and phenotypic divergence exists among WKY substrains from different sources [1] [3] [37]. Importantly, genetic divergence is not restricted to WKY controls: SHR substrains and lines from different breeders can also differ genetically and phenotypically [37]. Consequently, the designation "SHR" or "WKY" alone does not fully specify the experimental genotype, and provenance should be reported when interpreting or comparing results.

Differences among SHR and WKY substrains can alter the magnitude of observed strain contrasts and contribute to experimental heterogeneity [2] [37]. Interpretation should therefore recognize that part of the variability among studies may reflect differences in colony origin, substrain, or baseline phenotype, rather than hypertension *per se*. For reproducibility, studies should explicitly report the SHR and control substrain, breeder or colony source, sex, age, diet, and baseline blood-pressure characteristics [2] [37].

Beyond strain genetics, environmental and methodological variables also influence the SHR phenotype. Food composition, sodium intake, housing conditions, ambient temperature, enrichment, and microbiota can modify blood pressure and target-organ phenotypes [2] [43] [44]. Blood-pressure estimates can also vary according to measurement method and experimental conditions; SHR studies comparing noninvasive tail-cuff measurements with direct arterial recording have reported method-dependent differences, and wide limits of agreement [38]. Microbiome-related variability is increasingly supported by SHR-specific evidence: altered intestinal IgA responses and distinct IgA-coated microbial communities

have been reported in SHR [45] [46], while irbesartan-induced microbiota changes, and fecal microbiota transfer experiments indicate that microbial composition can modify blood pressure and host phenotypes in SHR [47]. Therefore, detailed standardization and reporting of these variables are essential for internal validity and reproducibility.

5.3. Biological Variables: Sex and Age

5.3.1. Sex as a Biological Variable: Sex-Dependent Hypertension and Target-Organ Injury

The predominance of male animals in the SHR literature limits generalizability to females. Direct SHR studies consistently show sex differences in blood-pressure regulation, with young adult males generally exhibiting higher arterial pressure than age-matched females [48] [49]. However, the hormonal basis of this difference is complex and should not be reduced to a simple model of estrogenic protection. Studies in SHR support important contributions from androgens and the renin-angiotensin system to the higher pressure observed in males [48]. Ovariectomy should therefore be described as an experimental model of ovarian-hormone/estrogen depletion, and not as biologically equivalent to natural menopause. Sex effects also vary with age, organ, and experimental context. Taken together, SHR studies support inclusion of both sexes and sex-stratified analyses whenever the research question permits.

5.3.2. The Age Factor: Hypertensive Steps and Senescence

Age is a major determinant of the SHR phenotype because blood pressure and target-organ remodeling develop progressively. Age ranges such as approximately 4 - 6 weeks for a prehypertensive/early phase, 6 - 12 weeks for evolving hypertension, and >12 weeks for established hypertension are commonly used experimental conventions, but they should not be regarded as universal biological thresholds [2]. The timing and magnitude of hypertension depend on substrain, sex, diet, colony conditions, and blood-pressure measurement method [2] [37] [38]. Similarly, changes observed in very old SHR reflect both, long-standing hypertension and aging itself. Thus, chronological age should be reported and interpreted together with the actual blood-pressure phenotype and organ-specific functional status, rather than used as a surrogate for disease stage.

5.4. Integration of Limitations in Translational Interpretation

The apparent paradox of the SHR is that one of its major strengths is also a translational limitation: relative absence of major metabolic comorbidities facilitates mechanistic study of pressure overload and neurohormonal regulation, but only partially represents hypertensive populations in which obesity, insulin resistance, dyslipidemia, or formal metabolic syndrome coexist [2]. The SHR should therefore not be considered a universal model of hypertension. Its value is greatest as a mechanistic model whose findings can be integrated with metabolically more complex models [39] [40]. Interpretation also requires explicit consideration of

substrain, sex, age, diet, environmental conditions, and blood-pressure measurement methods, because these factors influence the phenotype and can affect reproducibility [2] [37]. Accordingly, **Table 1** summarizes the suitability of the SHR for different research questions, highlighting both its major mechanistic strengths and the experimental or clinical contexts in which complementary models may be required.

Table 1. Suitability of SHR model according to the research question.

Scientific question	Usefulness	Justification
Cardiac remodeling due to pressure overload	✓ Yes	Spontaneous polygenic model that shows concentric hypertrophy and myocardial fibrosis [12].
Tissue-specific RAAS regulation	✓ Yes	SHR-specific studies demonstrate tissue- and stage-dependent RAAS regulation and partial dissociation between circulating and renal/cardiac angiotensin profiles [10] [11].
Oxidative stress and mitochondrial dysfunction	✓ Suitable	SHR hearts and kidneys show tissue- and stage-dependent mitochondrial remodeling and redox abnormalities, including changes in PGC-1alpha/dynamics and oxidative phosphorylation [18] [20] [21].
Cardiorenal fibrosis	✓ Yes	Cardiac and renal fibrosis are documented in SHR and can coexist with inflammatory/redox abnormalities; their temporal and causal sequence varies by tissue and disease stage [15] [30].
Hypertension + obesity	Limited/requires complementary model	The classic SHR is generally lean; consider an obese hypertensive strain such as SHROB or SHR/NDmcr-cp [2].
Hypertension + type 2 diabetes	✗ No	The classic SHR does not spontaneously develop overt type 2 diabetes; a combined hypertensive-diabetic model is required [2].
Metabolic syndrome full	✗ No	The classic SHR does not reproduce the full metabolic syndrome; consider an obese hypertensive model such as SHR/NDmcr-cp or SHROB [2] Corosolic acid prevents oxidative stress, inflammation and hypertension in SHR/NDmcr-cp rats, a model of metabolic syndrome [50].

6. Perspectives: Precision Phenotyping and Emergent Therapeutic Targets

Conventional molecular tools, such as directed qPCR and western blot of complete tissues, allowed to characterize the redox, inflammatory and fibrotic alterations in the SHR; however, these approaches average the signal of thousands of heterogeneous cells, then impeding the precise identification of which cellular populations initiate, sustain, or amplify the cardiorenal damage. In practice this means that we know the general mechanisms, but ignoring the exact responsible cellular architecture; to overcome this limitation needs to incorporate high resolution phenotyping technologies to search the SHR (**Figure 4**).

One persistent question in research on this model is which specific cell subpopulations within the SHR kidney and heart participate in the transition from adaptive remodeling to fibrosis. Single-cell transcriptomics (scRNA-seq) offers a direct way to address this question. Its use in SHR remains limited; however,

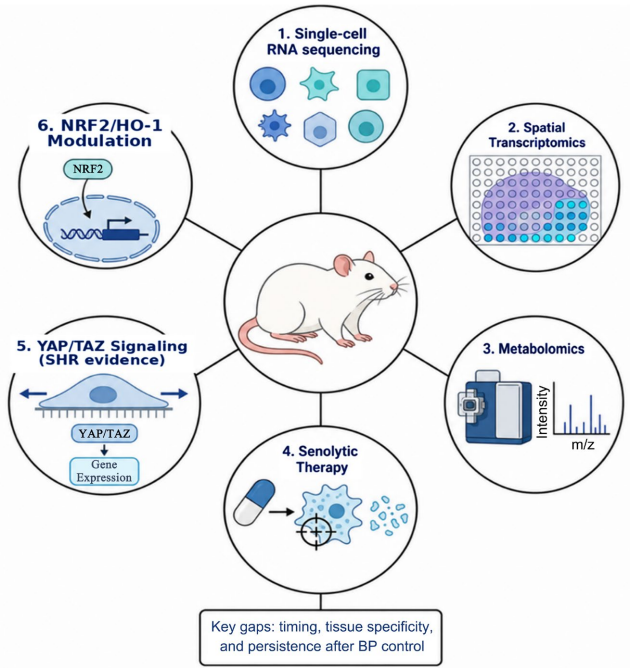

Figure 4. Strategic Framework for Future Research Directions in SHR. Emerging approaches to address current mechanistic gaps include: 1) single-cell transcriptomics; 2) spatial transcriptomics; 3) metabolomics; 4) targeted evaluation of cellular senescence; 5) Hippo/YAP/TAZ signaling, for which SHR renal and vascular intervention data are now available; and 6) NRF2/HO-1 modulation, which has already been pharmacologically manipulated in SHR. Key unresolved questions include tissue specificity, timing, causality, and persistence of remodeling after blood-pressure control. Source: Elaborated with https://www.lovart.ai.

studies in renal injury models have shown that tubulointerstitial fibrosis can involve specialized subpopulations of perivascular fibroblasts, and resident macrophages with profibrotic secretory phenotypes [51]. Applying scRNA-seq across SHR disease stages could define when and in which cell populations TGF-β/SMAD- and NF-κB-associated programs emerge. Spatial transcriptomics could add the anatomical context required to map these cell-cell interactions in peritubular and perivascular niches [52]. Such approaches would also allow direct testing of whether hypoxic stress and potentially altered venous hemodynamics converge in specific renal microenvironments, rather than assuming chronic renal venous congestion as an established feature of the SHR.

Nevertheless, changes in gene expression do not always translate in functional alterations of proteins or metabolites; this discrepancy between transcriptome and the functional phenotype represents a methodological void, such that high resolution proteomics and metabolomics could start closing it up.

Metabolic profiling has identified early metabolic abnormalities in SHR hearts during the development of hypertension, including changes in glucose metabolism and fatty acyl- and branched-chain amino-acid-derived carnitines [41]. More recently, plasma and urinary metabolomics in 16-week-old male SHR identified differential metabolites involving steroid-hormone, bile-acid, purine, and micro-

biota-associated metabolic pathways [42]. Integrating these metabolic data with transcriptomic and proteomic measurements may help determine whether reported mitochondrial, and NRF2-related changes have measurable functional counterparts in heart and kidney. Importantly, metabolomic associations should be interpreted as hypothesis-generating unless linked to intervention or longitudinal evidence.

Cellular senescence is another potentially relevant research axis, but SHR-specific evidence is tissue-dependent. In classic SHR, a longitudinal analysis reported increased expression of senescence-associated markers in the heart and liver across several ages, whereas the kidney did not show the same pattern [53]. Therefore, a generalized claim that renal tubular senescence is an established driver of cardiorenal injury in classic SHR would be premature. Studies in the stroke-prone SHR substrain have reported sex- and age-dependent senescence and fibrosis in heart and kidney, emphasizing that these findings can vary by substrain [54]. Senolytic therapy remains an attractive hypothesis, but whether selective elimination of senescent cells modifies spontaneous cardiorenal injury in classic SHR has not yet been established.

Mechanotransduction is an emerging link between mechanical load and tissue remodeling. Recent SHR-specific evidence supports involvement of Hippo/YAP signaling in hypertensive organ injury. Peptide 17 treatment and YAP silencing attenuated renal injury, inflammatory markers, and profibrotic signaling in SHR [55]. More recently, enhanced YAP/TAZ activation has been demonstrated in the SHR aorta in association with vascular smooth-muscle proliferation, fibrosis, and remodeling [56]. These studies justify investigation of YAP/TAZ as a therapeutic target in SHR; however, whether this pathway explains persistent cardiac or renal fibrosis after normalization of blood pressure remains unproven, and should be presented as a testable hypothesis.

Finally, pharmacological modulation of the NRF2/KEAP1 axis remains a relevant therapeutic research direction in SHR. Resveratrol has been shown to restore renal Nrf2 activity and reduce oxidative stress and inflammation in SHR [22]. In addition, a recent SHR study demonstrated that celastrol ameliorated renal injury while activating the Nrf2/HO-1 pathway, and reducing oxidative stress [23]. Thus, NRF2-related pathways have already been pharmacologically modulated in SHR, and the key unresolved questions concern timing, tissue specificity, durability, and whether early intervention can prevent progression to structural injury. Addressing these questions will require longitudinal designs that combine direct functional measurements with molecular and omics phenotyping.

Taken together, these approaches are not intended to replace the SHR model, but to increase the resolution with which its strengths and limitations are defined. Single-cell and spatial methods, metabolomics, direct mitochondrial phenotyping, and targeted interrogation of senescence, YAP/TAZ, NLRP3, and NRF2 pathways may generate testable hypotheses for subsequent validation in metabolically complex models and, ultimately, clinical studies. The distinction between demonstrated SHR mechanisms and hypotheses extrapolated from other disease contexts

should remain explicit throughout this process.

7. Conclusions

The SHR remains a valuable experimental model for essential hypertension and target-organ injury; however, its translational usefulness depends on specifying which mechanisms are directly supported in the model and which remain inferential. The SHR permits detailed study of sustained pressure overload, tissue-specific RAAS regulation, redox and inflammatory abnormalities, and progressive cardiac and renal remodeling. These processes are associated in the model, but their temporal and causal hierarchy is not uniform across tissues or disease stages. The relevance of SHR findings to human disease should therefore be assessed alongside evidence from metabolically and phenotypically diverse experimental models and clinical studies. In particular, the classic SHR does not reproduce the full cardiometabolic phenotype characterized by obesity, overt dysglycemia, and the clustering of metabolic abnormalities, thereby limiting direct extrapolation to patients with metabolic syndrome or obesity-associated hypertension.

The major strengths of the SHR are its spontaneous polygenic hypertension and progressive target-organ remodeling, without the need for a supraphysiological hypertensive stimulus. Cardiac and renal injury in this model should not be interpreted as a simple consequence of systemic blood pressure alone; rather, both organs are exposed to shared mechanical, neurohormonal, redox, inflammatory, and fibrotic influences. SHR-specific evidence of increased cardiac filling pressure and altered venous capacitance additionally raises the possibility that venous hemodynamics contribute to cardiorenal interaction, but sustained renal venous hypertension and chronic renal congestion have not been directly demonstrated in untreated SHR. Accordingly, venous congestion should remain a testable mechanistic hypothesis, rather than an established characteristic of the model. Translational interpretation must also account for the metabolic gap, variation among SHR and WKY substrains, sex and age effects, diet and environmental conditions, microbiome-related variability, and blood-pressure measurement methods.

Ultimately, the scientific value of the SHR lies in providing a high-resolution mechanistic framework, rather than reproducing the entire heterogeneity of human hypertension. Future work should use precise phenotyping and direct intervention studies to distinguish causal mechanisms from associations, particularly for mitochondrial remodeling, inflammasome activation, cellular senescence, mechanotransduction, and antioxidant pathways. Findings from SHR should then be integrated with metabolically complex animal models and clinical evidence. The appropriate experimental model should be selected according to the biological question it is designed to answer, not according to its ability to reproduce every component of the human syndrome.

Acknowledgements

MFPI was Ayudante de Investigador Nacional Emérito, SNII, CONAHCyT, México.

Funding

This work was supported by PAPIIT-DGAPA, UNAM, through grants IN228826 (IAGO) and IN228825, IN214627 (RVM).

Author Contributions

Conceptualization: M. F. I.-P.; investigation and literature review: M. F. I.-P.; writing—original draft preparation: M. F. I.-P.; writing—review and editing: I. A. G.-O., R. V.-M. and S. C. S.-F.; visualization and figure preparation: M. F. I.-P. and S. C. S.-F.; figure design and conceptualization: S. C. S.-F. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Okamoto, K. and Aoki, K. (1963) Development of a Strain of Spontaneously Hypertensive Rats. *Japanese Circulation Journal*, **27**, 282-293. https://doi.org/10.1253/jcj.27.282

[2] Lerman, L.O., Kurtz, T.W., Touyz, R.M., Ellison, D.H., Chade, A.R., Crowley, S.D., *et al.* (2019) Animal Models of Hypertension: A Scientific Statement from the American Heart Association. *Hypertension*, **73**, e87-e120. https://doi.org/10.1161/hyp.0000000000000090

[3] Kurtz, T.W. and Morris, R.C. (1987) Biological Variability in Wistar-Kyoto Rats. Implications for Research with the Spontaneously Hypertensive Rat. *Hypertension*, **10**, 127-131. https://doi.org/10.1161/01.hyp.10.1.127

[4] Kjeldsen, S.E., Naditch-Brule, L., Perlini, S., Zidek, W. and Farsang, C. (2008) Increased Prevalence of Metabolic Syndrome in Uncontrolled Hypertension across Europe: The Global Cardiometabolic Risk Profile in Patients with Hypertension Disease Survey. *Journal of Hypertension*, **26**, 2064-2070. https://doi.org/10.1097/hjh.0b013e32830c45c3

[5] Catharina, A.S., Modolo, R., Ritter, A.M.V., Sabbatini, A.R., Lopes, H.F., Moreno Junior, H., *et al.* (2018) Metabolic Syndrome-Related Features in Controlled and Resistant Hypertensive Subjects. *Arquivos Brasileiros de Cardiologia*, 110, 514-521. https://doi.org/10.5935/abc.20180076

[6] Rahmouni, K., Morgan, D.A., Morgan, G.M., Mark, A.L. and Haynes, W.G. (2005) Role of Selective Leptin Resistance in Diet-Induced Obesity Hypertension. *Diabetes*, **54**, 2012-2018. https://doi.org/10.2337/diabetes.54.7.2012

[7] Hall, J.E., do Carmo, J.M., da Silva, A.A., Wang, Z. and Hall, M.E. (2015) Obesity-Induced Hypertension. *Circulation Research*, **116**, 991-1006. https://doi.org/10.1161/circresaha.116.305697

[8] Sakitani, N. (2026) The Sympathetic Nervous System in the Pathophysiology of Hypertension: Mechanistic Insights and Therapeutic Implications. *Hypertension Research*, **49**, 1324-1328. https://doi.org/10.1038/s41440-026-02589-6

[9] Shiono, K. and Sokabe, H. (1976) Renin-angiotensin System in Spontaneously Hypertensive Rats. *American Journal of Physiology-Legacy Content*, **231**, 1295-1299. https://doi.org/10.1152/ajplegacy.1976.231.4.1295

[10] Grima, M., Ingert, C., Michel, B., Barthelmebs, M. and Imbs, J.L. (1997) Renal Tissue Angiotensins during Converting Enzyme Inhibition in the Spontaneously Hypertensive Rat. *Clinical and Experimental Hypertension*, **19**, 671-685. https://doi.org/10.3109/10641969709083178

[11] Nagano, M., Higaki, J., Mikami, H., Nakamaru, M., Higashimori, K., Katahira, K., *et al.* (1991) Converting Enzyme Inhibitors Regressed Cardiac Hypertrophy and Reduced Tissue Angiotensin II in Spontaneously Hypertensive Rats. *Journal of Hypertension*, **9**, 595-599. https://doi.org/10.1097/00004872-199107000-00003

[12] Frohlich, E.D. and Susic, D. (2012) Pressure Overload. *Heart Failure Clinics*, **8**, 21-32. https://doi.org/10.1016/j.hfc.2011.08.005

[13] Tolbert, E.M., Weisstuch, J., Feiner, H.D. and Dworkin, L.D. (2000) Onset of Glomerular Hypertension with Aging Precedes Injury in the Spontaneously Hypertensive Rat. *American Journal of Physiology-Renal Physiology*, **278**, F839-F846. https://doi.org/10.1152/ajprenal.2000.278.5.f839

[14] Rodríguez, J.E., Saucedo-Campos, A.D., Vega, A.V., Ramírez-Hernández, D., Martínez-Aguilar, L., Jiménez-Flores, J.R., *et al.* (2020) The α1D-Adrenoreceptor Antagonist BMY 7378 Reverses Cardiac Hypertrophy in Spontaneously Hypertensive Rats. *Journal of Hypertension*, **38**, 1496-1503. https://doi.org/10.1097/hjh.0000000000002412

[15] Shi, W., Guo, L., Liu, G., Peng, T., Li, H., Xie, T., *et al.* (2018) Protective Effect of Calcitriol on Podocytes in Spontaneously Hypertensive Rat. *Journal of the Chinese Medical Association*, **81**, 691-698. https://doi.org/10.1016/j.jcma.2018.01.010

[16] Forrester, S.J., Kikuchi, D.S., Hernandes, M.S., Xu, Q. and Griendling, K.K. (2018) Reactive Oxygen Species in Metabolic and Inflammatory Signaling. *Circulation Research*, **122**, 877-902. https://doi.org/10.1161/circresaha.117.311401

[17] Lassègue, B., San Martín, A. and Griendling, K.K. (2012) Biochemistry, Physiology, and Pathophysiology of NADPH Oxidases in the Cardiovascular System. *Circulation Research*, **110**, 1364-1390. https://doi.org/10.1161/circresaha.111.243972

[18] Tang, Y., Mi, C., Liu, J., Gao, F. and Long, J. (2014) Compromised Mitochondrial Remodeling in Compensatory Hypertrophied Myocardium of Spontaneously Hypertensive Rat. *Cardiovascular Pathology*, **23**, 101-106. https://doi.org/10.1016/j.carpath.2013.11.002

[19] Quiroga, C., Mancilla, G., Oyarzun, I., Tapia, A., Caballero, M., Gabrielli, L.A., *et al.* (2020) Moderate Exercise in Spontaneously Hypertensive Rats Is Unable to Activate the Expression of Genes Linked to Mitochondrial Dynamics and Biogenesis in Cardiomyocytes. *Frontiers in Endocrinology*, **11**, Article No. 546. https://doi.org/10.3389/fendo.2020.00546

[20] Natarajan, B., Arige, V., Khan, A.A., Reddy, S.S., Barthwal, M.K. and Mahapatra, N.R. (2020) Hypoxia-Mediated Regulation of Mitochondrial Transcription Factors in Renal Epithelial Cells: Implications for Hypertensive Renal Physiology. *Hypertension Research*, **44**, 154-167. https://doi.org/10.1038/s41440-020-00539-4

[21] Mujkošová, J., Uličná, O., Waczulíková, I., Vlkovičová, J., Vančová, O., Ferko, M., *et al.* (2010) Mitochondrial Function in Heart and Kidney of Spontaneously Hypertensive Rats: Influence of Captopril Treatment. *General Physiology and Biophysics*, **29**, 203-207. https://doi.org/10.4149/gpb_2010_02_203

[22] Javkhedkar, A.A., Quiroz, Y., Rodriguez-Iturbe, B., Vaziri, N.D., Lokhandwala, M.F. and Banday, A.A. (2015) Resveratrol Restored Nrf2 Function, Reduced Renal Inflammation, and Mitigated Hypertension in Spontaneously Hypertensive Rats. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **308**,

R840-R846. https://doi.org/10.1152/ajpregu.00308.2014

[23] Deng, Y., Wang, J., Liu, X., Wang, X., Li, H., Gu, B., *et al.* (2026) Celastrol Ameliorates Renal Injury in Spontaneously Hypertensive Rats by Activating the Nrf2/HO-1 Signaling Pathway to Alleviate Oxidative Stress. *International Journal of Molecular Sciences*, **27**, Article No. 3849. https://doi.org/10.3390/ijms27093849

[24] Liu, T., Zhang, L., Joo, D. and Sun, S. (2017) NF-κB Signaling in Inflammation. *Signal Transduction and Targeted Therapy*, **2**, Article No. 17023. https://doi.org/10.1038/sigtrans.2017.23

[25] Madhur, M.S., Elijovich, F., Alexander, M.R., Pitzer, A., Ishimwe, J., Van Beusecum, J.P., *et al.* (2021) Hypertension: Do In-flammation and Immunity Hold the Key to Solving This Epidemic? *Circulation Research*, **128**, 908-933. https://doi.org/10.1161/circresaha.121.318052

[26] Chen, D., Xiong, X., Zang, Y., Tong, Y., Zhou, B., Chen, Q., *et al.* (2017) BCL6 Attenuates Renal Inflammation via Negative Regulation of NLRP3 Transcription. *Cell Death & Disease*, **8**, e3156. https://doi.org/10.1038/cddis.2017.567

[27] Ge, C., Zhao, Y., Liang, Y. and He, Y. (2022) Silencing of TLR4 Inhibits Atrial Fibrosis and Susceptibility to Atrial Fibrillation via Downregulation of NLRP3-TGF-β in Spontaneously Hypertensive Rats. *Disease Markers*, **2022**, Article ID: 2466150. https://doi.org/10.1155/2022/2466150

[28] Meng, X., Tang, P.M., Li, J. and Lan, H.Y. (2015) TGF-β/Smad Signaling in Renal Fibrosis. *Frontiers in Physiology*, **6**, Article No. 82. https://doi.org/10.3389/fphys.2015.00082

[29] Leask, A. and Abraham, D.J. (2004) TGF-Beta Signaling and the Fibrotic Response. *The FASEB Journal*, **18**, 816-827. https://doi.org/10.1096/fj.03-1273rev

[30] Zhang, Y., Ma, J., Wei, F., Gong, J., Zhuang, L., Zhang, N., *et al.* (2024) Polyenylphosphatidylcholine Alleviates Cardiorenal Fibrosis, Injury and Dysfunction in Spontaneously Hypertensive Rats by Regulating Plpp3 Signaling. *Frontiers in Cardiovascular Medicine*, **11**, Article ID: 1458173. https://doi.org/10.3389/fcvm.2024.1458173

[31] Ronco, C., Haapio, M., House, A.A., Anavekar, N. and Bellomo, R. (2008) Cardiorenal Syndrome. *Journal of the American College of Cardiology*, **52**, 1527-1539. https://doi.org/10.1016/j.jacc.2008.07.051

[32] Mullens, W., Abrahams, Z., Francis, G.S., Sokos, G., Taylor, D.O., Starling, R.C., *et al.* (2009) Importance of Venous Congestion for Worsening of Renal Function in Advanced Decompensated Heart Failure. *Journal of the American College of Cardiology*, **53**, 589-596. https://doi.org/10.1016/j.jacc.2008.05.068

[33] Emans, T.W., Moraes, D.J.A., Ben-Tal, A., Barrett, C.J., Paton, J.F.R. and McBryde, F.D. (2024) Forgotten Circulation: Reduced Mesenteric Venous Capacitance in Hypertensive Rats Is Improved by Decreasing Sympathetic Activity. *Hypertension*, **81**, 823-835. https://doi.org/10.1161/hypertensionaha.123.21878

[34] Fu, L., Ruan, Q., You, Z., Huang, H., Chen, Y., Cheng, S., *et al.* (2022) Investigation of Left Ventricular Strain and Its Morphological Basis during Different Stages of Diastolic and Systolic Dysfunction in Spontaneously Hypertensive Rat. *American Journal of Hypertension*, **35**, 423-432. https://doi.org/10.1093/ajh/hpac008

[35] Zhou, B., Zhao, J. and Li, D. (2024) A New Animal Model of Cardiorenal Syndrome Could Be Established by Inducing Heart Failure through Coronary Artery Ligation in Spontaneously Hypertensive Rats. *Scientific Reports*, **14**, Article No. 18732. https://doi.org/10.1038/s41598-024-69662-3

[36] Navar, L.G. (2005) The Role of the Kidneys in Hypertension. *The Journal of Clinical Hypertension*, **7**, 542-549. https://doi.org/10.1111/j.1524-6175.2005.04130.x

[37] Zhang-James, Y., Middleton, F.A. and Faraone, S.V. (2013) Genetic Architecture of Wistar-Kyoto Rat and Spontaneously Hypertensive Rat Substrains from Different Sources. *Physiological Genomics*, **45**, 528-538. https://doi.org/10.1152/physiolgenomics.00002.2013

[38] Ibrahim, J., Berk, B.C. and Hughes, A.D. (2006) Comparison of Simultaneous Measurements of Blood Pressure by Tail-Cuff and Carotid Arterial Methods in Conscious Spontaneously Hypertensive and Wistar-Kyoto Rats. *Clinical and Experimental Hypertension*, **28**, 57-72. https://doi.org/10.1080/10641960500386817

[39] Reaven, G.M., Twersky, J. and Chang, H. (1991) Abnormalities of Carbohydrate and Lipid Metabolism in Dahl Rats. *Hypertension*, **18**, 630-635. https://doi.org/10.1161/01.hyp.18.5.630

[40] Aitman, T.J., Gotoda, T., Evans, A.L., Imrie, H., Heath, K.E., Trembling, P.M., *et al.* (1997) Quantitative Trait Loci for Cellular Defects in Glucose and Fatty Acid Metabolism in Hypertensive Rats. *Nature Genetics*, **16**, 197-201. https://doi.org/10.1038/ng0697-197

[41] Li, J., Kemp, B.A., Howell, N.L., Massey, J., Mińczuk, K., Huang, Q., *et al.* (2019) Metabolic Changes in Spontaneously Hypertensive Rat Hearts Precede Cardiac Dysfunction and Left Ventricular Hypertrophy. *Journal of the American Heart Association*, **8**, e010926. https://doi.org/10.1161/jaha.118.010926

[42] Rodríguez-Pérez, C., Vázquez-Aguilar, A., Rangel Huerta, O.D., Sánchez-Rodríguez, E., Gil, Á., Díaz, C., *et al.* (2026) New Insights into the Plasma and Urinary Metabolomic Signatures of Spontaneously Hypertensive Rats. *PLOS ONE*, **21**, e0344682. https://doi.org/10.1371/journal.pone.0344682

[43] Yang, T., Richards, E.M., Pepine, C.J. and Raizada, M.K. (2018) The Gut Microbiota and the Brain-Gut-Kidney Axis in Hypertension and Chronic Kidney Disease. *Nature Reviews Nephrology*, **14**, 442-456. https://doi.org/10.1038/s41581-018-0018-2

[44] Santisteban, M.M., Qi, Y., Zubcevic, J., Kim, S., Yang, T., Shenoy, V., *et al.* (2017) Hypertension-Linked Pathophysiological Alterations in the Gut. *Circulation Research*, **120**, 312-323. https://doi.org/10.1161/circresaha.116.309006

[45] Saha, P., Mell, B., Golonka, R.M., Bovilla, V.R., Abokor, A.A., Mei, X., *et al.* (2022) Selective IgA Deficiency in Spontaneously Hypertensive Rats with Gut Dysbiosis. *Hypertension*, **79**, 2239-2249. https://doi.org/10.1161/hypertensionaha.122.19307

[46] Li, J., Richards, E.M., Tummala, R., Pepine, C.J., Raizada, M.K. and Yang, T. (2023) Host-Microbiota Communication in Spontaneously Hypertensive Rats Generates Unique IgA-Coated Gut Microbes. *Journal of the American Heart Association*, **12**, e027918. https://doi.org/10.1161/jaha.122.027918

[47] Xiong, Y., He, Y., Chen, Z., Wu, T., Xiong, Y., Peng, Y., *et al.* (2023) Lactobacillus Induced by Irbesartan on Spontaneously Hypertensive Rat Contribute to Its Antihypertensive Effect. *Journal of Hypertension*, **42**, 460-470. https://doi.org/10.1097/hjh.0000000000003613

[48] Reckelhoff, J.F., Zhang, H. and Srivastava, K. (2000) Gender Differences in Development of Hypertension in Spontaneously Hypertensive Rats: Role of the Ren-in-Angiotensin System. *Hypertension*, **35**, 480-483. https://doi.org/10.1161/01.hyp.35.1.480

[49] Moulana, M., Hosick, K., Stanford, J., Zhang, H., Roman, R.J. and Reckelhoff, J.F. (2014) Sex Differences in Blood Pressure Control in SHR: Lack of a Role for EETs.

Physiological Reports, **2**, e12022. https://doi.org/10.14814/phy2.12022

[50] Yamaguchi, Y., Yamada, K., Yoshikawa, N., Nakamura, K., Haginaka, J. and Kunitomo, M. (2006) Corosolic Acid Prevents Oxidative Stress, Inflammation and Hypertension in SHR/NDmcr-cp Rats, a Model of Metabolic Syndrome. *Life Sciences*, **79**, 2474-2479. https://doi.org/10.1016/j.lfs.2006.08.007

[51] Kuppe, C., Ibrahim, M.M., Kranz, J., Zhang, X., Ziegler, S., Perales-Patón, J., *et al.* (2021) Decoding Myofibroblast Origins in Human Kidney Fibrosis. *Nature*, **589**, 281-286. https://doi.org/10.1038/s41586-020-2941-1

[52] Rao, A., Barkley, D., França, G.S. and Yanai, I. (2021) Exploring Tissue Architecture Using Spatial Transcriptomics. *Nature*, **596**, 211-220. https://doi.org/10.1038/s41586-021-03634-9

[53] Somsura, R., Kamkajon, K., Chaimongkolnukul, K., Chantip, S., Teerapornpuntakit, J., Wongdee, K., *et al.* (2023) Tissue-Specific Expression of Senescence Biomarkers in Spontaneously Hypertensive Rats: Evidence of Premature Aging in Hypertension. *PeerJ*, **11**, e16300. https://doi.org/10.7717/peerj.16300

[54] Ansari, A., Walton, S.L. and Denton, K.M. (2023) Sex- and Age-Related Differences in Renal and Cardiac Injury and Senescence in Stroke-Prone Spontaneously Hypertensive Rats. *Biology of Sex Differences*, **14**, Article No. 33. https://doi.org/10.1186/s13293-023-00519-6

[55] Xu, S., Xu, B., Ma, Z., Huang, M., Gao, Z. and Ni, J. (2022) Peptide 17 Alleviates Early Hypertensive Renal Injury by Regulating the Hippo/YAP Signalling Pathway. *Nephrology*, **27**, 712-723. https://doi.org/10.1111/nep.14066

[56] Bai, J. and Yang, Y. (2025) Activation of Hippo/YAP Signaling Pathway Exacerbates Vascular Remodeling and Aggravates Hypertension by Upregulating Foxm1. *Journal of Molecular Histology*, **56**, Article No. 158. https://doi.org/10.1007/s10735-025-10443-1