

Analogy of Cardiac and Renal Complications in Essential Hypertension and Aged SHR or L-NAME/SHR

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Abstract: Hypertension plays major causative roles in development of cardiac failure and end-stage renal disease (ESRD). Cardiac and renal involvements in hypertension and relevant pharmacological interventions have been extensively studied in our laboratories. Our findings demonstrated that aged spontaneous hypertensive rats (SHR) developed reduced coronary flow reserve, increased coronary vascular resistance and cardiac fibrosis, and impaired cardiac function. Moreover, aged SHR naturally developed glomerular hypertension and ischemia, proteinuria, and glomerular sclerosis and interstitial fibrosis. These naturally-occurring cardiac and renal involvements in aged SHR are very similar to these target organ changes in essential hypertension. Furthermore, we have been able to reproduce similar derangements in younger adult SHR by nitric oxide synthesis inhibition. These changes are identical to the pathophysiological alterations in heart and kidney found in old SHR as well as clinically. Antihypertensive therapeutic interventions provided cardiac and renal protection and, perhaps even prevention in the aged SHR and younger adult SHR with suppressed nitric oxide synthesis. Recent clinical trails have translated these pathophysiological observations demonstrating that angiotensin II inhibition affords remarkable cardiac and renal benefits to patients with essential hypertension.

Thus, both the aged SHR as well as younger adult SHR with suppressed nitric oxide synthesis very closely mimic the cardiac and renal outcomes seen in patients with essential hypertension. They accordingly have become extremely useful experimental models of hypertensive heart disease and ESRD seen with severe nephrosclerosis. The latter hypertensive rat model with induced endothelial dysfunction is recommended enthusiastically for its foregoing as well as time-saving and economic values.

Key Words: Hypertension, cardiac failure, end-stage renal disease, experimental model.

INTRODUCTION

Hypertension is a major health problem affecting approximately one billion people worldwide; and it plays an important causative role in the development of cardiac failure, end-stage renal disease (ESRD), and strokes [1, 2]. Although morbidity and mortality from stroke have been dramatically decreased by arterial pressure reduction [3], the prevalence of cardiac failure and ESRD in hypertension continues to increase progressively to remain major disabilities and causes of death [4-6]. It follows then that investigation of the fundamental mechanisms underlying hypertension induced cardiac and renal damage and of the most appropriate treatments, experimentally and clinically, still remains critical importance.

Clinical studies have demonstrated that ventricular ischemia [7-9], fibrosis [10-12], and apoptosis [13, 14] are the key underlying pathophysiological mechanistic epiphenomena associated with hypertensive heart disease (HHD). Whereas glomerular hypertension with progressional glomerular sclerosis as well as ischemia, fibrosis, and apoptosis is associated with the hypertension-induced ESRD [15-17]. Recently, our experimental studies of the spontaneously hypertensive rats (SHR) have demonstrated a striking and meaningful

analogy of the cardiac and renal outcomes between essential hypertension and elderly SHR or younger adult SHR with nitric oxide synthesis inhibition by N^o-nitro-L-arginine-methyl-ester (L-NAME) [18-20]. This review emphasizes the cardiac and renal pathophysiological alterations in these experimental models of hypertension, their responses to newer antihypertensive therapy, and their clear-cut relevance to clinical essential hypertension.

AGED SHR AND ITS CARDIOVASCULAR AND RENAL ALTERATIONS

The SHR is an excellent model that is highly analogous to essential hypertension in man [21]. Earlier studies from our laboratory and others have demonstrated that the natural progression of cardiac and renal complications of sustained arterial hypertension and aging in SHR are remarkably analogous to clinical hypertension [22-26]. The aged SHR exhibited reduced coronary flow reserve, higher coronary and renal vascular resistance, impaired left ventricular and renal functions, and increased ventricular and renal fibrosis and apoptosis [22-26]. Obviously, these alterations are similar in both target organs of the disease and are akin to the findings in patients with essential hypertension with HHD and ESRD [7-17]. Consequently, the aged SHR can be considered as an ideal experimental model for naturally developing HHD and ESRD. However, to maintain younger SHR until old age (older than 6 to 12 months) is extremely costly and time-consuming and, hence, requires a more practical modification of this experimental model.

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THE L-NAME/SHR MODEL AND ITS CARDIO-RENAL CHANGES

Nitric oxide, an endogenous endothelial vasodilating substance, plays a critical role in regulating endothelial function of systemic and organic vascular beds [27-29]. Inhibition of the action of the enzyme nitric oxide synthase by L-NAME has been shown to increase sympathetic nervous activity [30] and activate the systemic and local renin-angiotensin systems [30-32]. Moreover, the sympathetic nervous and renin-angiotensin systems act as fundamental mechanisms that promote persistent hypertension and progressive cardiovascular and renal damage in animal model and human beings [33-39]. Based on this compelling experimental and clinical evidence, we developed and established the L-NAME/SHR model by prolonged administration of the nitric oxide synthase enzymatic inhibitor L-NAME to younger adult SHR (17-week-old) for three weeks [18-20]. This intervention mimics the pathophysiological alterations associated with naturally-occurring progressive impairment of cardiac and renal function and structure in the aged SHR [18, 40, 41]. To this end, we have found an ideal model for cardiac [40] and renal [18, 41] involvement in naturally-occurring hypertension.

Cardiac responses to prolonged nitric oxide synthesis inhibition have been investigated in SHR following three weeks administration of L-NAME (using either of two doses, 50 mg/L and 80 mg/L in drinking water) [40]. The L-NAME/SHR developed severe HHD associated with severe interstitial fibrosis, small myocardial infarctions as well as impaired systemic and cardiac hemodynamics [40]. Histologically, the increased left ventricular mass (of left ventricular hypertrophy) is also associated with interstitial fibrosis, increased smooth muscular cell apoptosis, ventricular remodelings, myocardial infarction, coronary arterial medial hypertrophy, and severe arteriolar injury. Furthermore, these alterations were dose-dependent. Our data strongly suggested that coronary endothelial dysfunction and myocardial ischemia induced by the L-NAME were responsible for all the above-mentioned pathological findings and consequently, for the impaired function. These experimental findings are consistent with what is observed in clinical hypertensive heart disease [7-14].

The renal hemodynamic, glomerular dynamic, and histological responses to prolonged nitric oxide synthesis inhibition in younger adult SHR have been the subjects of our investigations for over 10 years [18, 20]. Our data have clearly demonstrated that L-NAME produced massive proteinuria associated with intensive afferent and efferent glomerular arteriolar constriction, significantly reduced renal blood flow, and glomerular hypertension with an increased filtration fraction. Histologically, the afferent arterioles revealed severe fibrinoid necrosis, segmental glomerular hyalinosis and sclerosis, and apoptosis [18, 41]. Furthermore, the relationship between apoptosis and glomerular injury was evaluated in two different L-NAME doses (50 mg/L or 80 mg/L) [41]. These data demonstrated that L-NAME (in both doses) induced not only increased glomerular cell apoptosis but also decreased intraglomerular cell numbers, increased mesangial matrix, and increased glomerular injury scores, which were

remarkably consistent with those alterations that we have observed earlier in the naturally-developing severe nephrosclerosis of aged (73 weeks old) SHR [25]. Therefore, we propose that the L-NAME/SHR has become an extremely useful and reproducible experimental model of severe nephrosclerosis in hypertension [18-20].

THERAPEUTICAL INTERVENTIONS

Antihypertensive Therapy In Aged SHR Rats

A number of studies have examined the effects of various antihypertensive therapies on cardiovascular structures and functions in aged SHR rats [25, 42-44]. In one study, we demonstrated that either the calcium antagonist felodipine or the angiotensin-converting enzyme (ACE) inhibitor enalapril, administered for 12 weeks, significantly improved the cardiovascular functional responses from hypertension in 77-week-old SHR rats, as evidenced by reduced arterial pressure, decreased left ventricular mass, and increased coronary flow reserve [42]. In addition, enalapril also reduced aortic mass and left ventricular collagen concentration, appearing to be more effective in improving coronary hemodynamics than felodipine, possibly because of its ability to reduce myocardial and, perhaps, perivascular fibrosis. In another study, we examined the effects of L-arginine, the nitric oxide precursor amino acid, on coronary hemodynamics and cardiac fibrosis in 80-week-old SHR rats. These data demonstrated that prolonged (6 months) administration of L-arginine diminished arterial pressure, total peripheral resistance, and left ventricular and aortic mass indices; and it also increased coronary flow reserve, reduced minimal coronary flow resistance and left ventricular collagen content, suggesting a striking cardiac protective effect of the nitric oxide precursor [43]. To support our findings, Li *et al.* reported that administration for 27 days (average) of the ACE inhibitor captopril ameliorated cardiac failure associated with a reduction in myocardial apoptosis in aged (18-24 months) SHR rats [24].

In accord with these therapeutic cardiac benefits, our earlier studies demonstrated that quinapril, an ACE inhibitor [25], or L-arginine [44] significantly increased glomerular filtration rate, markedly reduced glomerular and arteriolar injury scores as well as urinary protein excretion in 73-week-old or 85-week-old SHR. In another report, the angiotensin II type1 (AT1) receptor antagonist losartan (treatment for 55 weeks) normalized arterial pressure, prevented proteinuria and renal insufficiency, increased renal nitric oxide synthases protein contents, mitigated renal nitrotyrosine accumulation, and prevented the histological abnormalities in 63-week-old SHR rats [26]. These findings indicated therapeutic benefits provided by the nitric oxide precursor and angiotensin II inhibitors on kidney in aged SHR rats [25, 26, 44].

Antihypertensive Therapy In L-NAME/SHR Model

Using the L-NAME/SHR model, we have reported a series of studies designed to investigate the effects of several classes of antihypertensive agents on the prevention, development, progression and even reversal of hypertensive nephrosclerosis [45-51]. Each report documented the pathophysiological actions by the intervention of an antihypertensive agent either concomitantly with L-NAME or subsequently following L-NAME for a period of 3 weeks in male, adult 20

to 23 weeks old SHR. They also demonstrated that each class of pharmacological agent for three weeks significantly reduced left ventricular mass. On the other hand, the most intriguing and pertinent findings derived from our renal micropuncture studies on the renal hemodynamic and pathophysiological effects of calcium antagonists, ACE inhibitors, AT1 receptor antagonists, or aldosterone antagonists in L-NAME/SHR rats are detailed in the ensuing discussions.

Three different pharmacological and structural types of calcium antagonists, including L- (felodipine and amlodipine), T- (mibefradil), and N- (cilnidipine) types, were investigated [45-47]. Each of these agents dilated not only the afferent but also efferent glomerular arterioles, improved single nephron plasma flow and glomerular filtration rate in these SHR rats co-treated with L-NAME (representing the preventive effects of these calcium antagonists) as well as when they were given after L-NAME (signifying their reversing effects) [45-47]. These agents also prevented and reversed the glomerular and arteriolar injuries in this L-NAME/SHR model. In general, although there were some minor differences in the responses among these calcium antagonists, they did not differ substantially with respect to their overall renoprotective effects.

To investigate the renal effects of ACE inhibitors or AT1 receptor antagonist, we have studied quinapril, enalapril, lisinopril or candesartan in the L-NAME/SHR rats [45, 48-50]. Each of these pharmacological agents dilated both afferent and efferent glomerular arterioles, reduced glomerular capillary hydrostatic pressure, and prevented as well as reversed the development of proteinuria, hypercreatininemia, hyperuricemia, glomerular sclerosis, and arteriolar hyaline. Our data further demonstrated that AT1 receptor antagonism and ACE inhibition had very similar effects on renal hemodynamics and histopathology, and that the ACE inhibition of bradykinin degradation provided little evidence in support of a bradykinin renoprotective action in this model, suggesting that both classes of angiotensin II antagonists were equally effective in renoprotection in the L-NAME/SHR model [50]. Moreover, our recent data demonstrated that marked superiority of combination of thiazide with enalapril and/or losartan over thiazide alone on renoprotection in this model [51]. These findings provided strong evidence that angiotensin II plays a crucial role in development of hypertensive nephrosclerosis.

In addition, owing to the resurgence of the role of aldosterone as a deteriorating factor in hypertension and cardiac and renal injury [52, 53], we tested the effects of the aldosterone antagonist eplerenone in L-NAME-exacerbated SHR nephrosclerosis and the outcomes of combined therapy of eplerenone with the ACE-I lisinopril to determine whether aldosterone antagonism enhanced the effectiveness of ACE inhibition [49]. Our findings demonstrated that the aldosterone antagonist provided no effect on systemic, renal hemodynamics, or glomerular dynamics. However, it did markedly reduce the severe proteinuria and dramatically improved glomerular and arteriolar injuries and tubulointerstitial lesions in L-NAME/SHR, suggesting that its beneficial effects were most likely achieved through nonhemodynamic effects (e.g., its antiinflammatory or other actions) [54]. Combined

therapy of the aldosterone antagonist with an ACE-I produced no further renal benefits than the ACE-I alone.

Antihypertensive Therapy In Patients With Cardiac And Renal Complications Of Hypertension

Accumulated findings from clinical trials have demonstrated clearly that pharmacological intervention, particularly by angiotensin II inhibition, successfully reduces cardiac mortality and morbidity [55-64]. For examples, the survival and ventricular enlargement (SAVE) trial demonstrated that long-term administration of captopril improved survival and reduced morbidity and mortality due to major cardiovascular events in patients with left ventricular dysfunction after myocardial infarction [55]. The Studies of Left Ventricular Dysfunction (SOLVD) trial reported that enalapril significantly reduced the incidence of heart failure and the rate of related hospitalizations among patients with asymptomatic left ventricular dysfunction [56]. The Heart Outcomes Prevention Evaluation (HOPE) Study demonstrated that ramipril significantly reduces the rate of development of cardiac and renal failure in patients at high risk of cardiovascular events [58, 59]. The Candesartan in Heart failure-Assessment of Reduction in Mortality and Morbidity (CHARM) study reported that candesartan significantly reduced cardiovascular deaths and hospital admissions in patients with heart failure [60-64]. Of note, although not all patients included in the HOPE and CHARM trials had hypertension, this disease was one of the most common conditions predicting congestive heart failure [65]. In our review of the latest data of physiological evidence of renoprotection by antihypertensive therapy [66], the clinical studies have clearly demonstrated renoprotective effects of inhibition of renin-angiotensin-aldosterone system in patients with hypertension and chronic kidney disease [67, 68]. To date, the ACE inhibition and AT1 receptor blockade seem to provide equivalent renal benefits, although their dual blockade of renin-angiotensin system may confer greater renoprotection.

SUMMARY

Experimental studies have demonstrated that naturally-occurring cardiac and renal damage from hypertension in aged SHR are similar to the cardiac and renal alterations in younger adult SHR with prolonged nitric oxide synthesis inhibition. Both the aged SHR and L-NAME/SHR closely mimic the pathophysiological findings of essential hypertension with HHD and/or ESRD. Thus, they may be considered as ideal experimental models of hypertension with major target organs damage. We suggest that the L-NAME/SHR model provides the distinct advantages of time and cost effectiveness by targeting the marked endothelial dysfunction that occurs in essential hypertension. Convincing evidence from our series of reports has repeatedly confirmed that ischemia, fibrosis, and apoptosis are common pathophysiological alterations in this model, reflecting the hypertension-induced cardiac and renal damage in patients with essential hypertension. Moreover, our studies involving pharmacological interventions by various antihypertensive agents have demonstrated the remarkable cardiac and renal protective actions (notably those by angiotensin II inhibition). These studies supported by recent clinical trials have been presented to detail their promising therapeutic and preventive implications.

ABBREVIATIONS

ESRD	=	End-stage renal disease
HHD	=	Hypertensive heart disease
SHR	=	Spontaneously hypertensive rats
L-NAME	=	N ^o -nitro-L-arginine-methyl-ester
ACE	=	Angiotensin-converting enzyme
ATI	=	Angiotensin II type1

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