Renin-Angiotensin System Blockade Is Associated with Exercise Capacity, Sympathetic Activity, and Endothelial Function in Patients with Chronic Kidney Disease

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Keywords

Renin-angiotensin system · Exercise capacity · Sympathetic activity · Endothelial dysfunction · Chronic kidney disease

Abstract

Background: Chronic kidney disease (CKD) patients have exercise intolerance and exaggerated blood pressure reactivity during exercise that are mediated by sympathetic nervous system (SNS) overactivation and decreased nitric oxide (NO) bioavailability. The activation of the renin-angiotensin system (RAS) increases SNS activation and reduces NO synthesis, and prior studies suggest that RAS blockade attenuates declines in physical function. We hypothesized that RAS inhibitor (RASi) use is associated with higher exercise capacity mediated by decreased SNS activity and increased NO-dependent endothelial function in CKD. **Method:** In 35 CKD patients (57 ± 7 years) and 20 controls (CONs) (53 ± 8 years), we measured exercise capacity (peak oxygen consumption [VO_{2peak}]), muscle sympathetic nervous activity (MSNA), and flow-mediated dilation (FMD) for NO-dependent endothelial function. **Results:** CKD patients treated with RASi (CKD + RASi, n = 25) had greater VO_{2peak} than CKD patients not treated with RASi (CKD no RASi, n = 10), but lower VO_{2peak} than

CONs (23.3 ± 5.8 vs. 16.4 ± 2.9, p = 0.007; vs. 30.0 ± 7.7, p = 0.016 mL/min/kg, respectively). CKD + RASi had lower resting MSNA and greater FMD than CKD no RASi. Compared to CONs, CKD + RASi had similar MSNA but lower FMD. VO_{2peak} was positively associated with FMD (r = 0.417, p = 0.038) and was predicted by the combination of FMD and RASi status (r² = 0.344, p = 0.01) and MSNA and RASi status (r² = 0.575, p = 0.040) in CKD patients. **Conclusion:** In summary, CKD patients with RASi have higher exercise capacity than those not on RASi. Higher exercise capacity in the RASi-treated group was associated with lower resting SNS activity and higher NO-dependent vascular endothelial function.

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Introduction

Patients with chronic kidney disease (CKD) have decreased exercise capacity that begins in the early stages of disease development [1, 2]. This exercise intolerance is associated with an increased risk of cardiovascular (CV) events, all-cause mortality [3–5], and progression of CKD [6, 7], and contributes to worsening of quality of life [8]. The causes of exercise intolerance in CKD are complex

and likely multifactorial due to a number of CKD-associated complications, including uremic myopathy, neuropathy, anemia, metabolic acidosis, chronic overactivation of the sympathetic nervous system (SNS), and endothelial dysfunction [9–11]. We have previously shown that CKD patients have abnormal hemodynamic and neurocirculatory responses during exercise, including an exaggerated increase in blood pressure (BP). These responses are mediated, in part, by SNS overactivation [12] and decreased endothelial nitric oxide (NO) bioavailability [13].

The renin-angiotensin system (RAS) plays an important role in various physiological processes including BP control and tissue perfusion, and RAS activation is implicated in the pathogenesis of hypertension (HTN) and CV target organ damage [14–16]. Pharmacological blockade of RAS activity through angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) is commonly used in CKD for BP control and proteinuria [17, 18], although not universally prescribed in all CKD patients, particularly in those without proteinuria [19]. Interestingly, in addition to CV and renal effects, evidence suggests that RAS may also modulate physical function declines in populations with physical functional impairment. For example, one observational study suggests that older adults treated with ACEis exhibited attenuation in age-related reductions in physical capacity compared to their peers not treated with ACEis [20]. Additionally, randomized controlled trials have revealed that ACEi or ARB treatment improves exercise capacity and exercise duration in older adults [21, 22]. Beneficial effects of RAS blockade on physical function have also been documented in clinical populations including heart failure [23, 24] and peripheral artery disease [25]. However, the potential beneficial effects of RAS inhibition on physical function in CKD, on another patient population that is similarly characterized by exercise intolerance, have not been previously explored. Moreover, the mechanisms by which RAS blockade might mediate improvement in exercise capacity currently remain to be clarified.

RAS inhibition may positively impact exercise capacity through 2 distinct mechanisms: (1) modulation of SNS activity and (2) improvements in vascular endothelial function. CKD is characterized by both SNS overactivity at rest and during exercise [12, 26], as well as endothelial dysfunction that is linked to reduced exercise capacity [10, 13]. RAS activation increases SNS activity [27, 28], stimulates the production of reactive oxygen species, and suppresses the synthesis of potent vasodilators such as NO, which collectively promote endothelial dysfunction [29]. Decreased NO in turn also contributes to an in-

creased central SNS output [30]. Thus, blockade of RAS by using RAS inhibitors (RASis) has been shown to ameliorate SNS hyperactivity [26, 31] and improve endothelial function [32, 33]. Both of these may improve skeletal muscle blood flow regulation during exercise, thereby contributing to improvements in physical function. The purpose of this study was to investigate (1) the potential modulating effect of RASi on exercise capacity and (2) the potential physiological mechanisms of RASi effects on exercise capacity in patients with CKD. We hypothesized that the use of RASis is associated with greater exercise capacity in patients with CKD, which is in part mediated by lower SNS activity and increased NO-dependent vascular endothelial function.

Methods

Study Population

Fifty-five sedentary participants including 35 CKD patients and 20 age-matched controls (CONs) were recruited and enrolled from outpatient clinics at the Atlanta Veterans Affairs (VA) Healthcare System. All participants with CKD had a confirmed diagnosis of either stage 2 (estimated glomerular filtration rate [eGFR] of 60–89 mL min⁻¹ 1.73 m⁻² with a concomitant urinary microalbumin:creatinine ratio of >30 mg/g) or stage 3 (eGFR of 30–59 mL min⁻¹ 1.73 m⁻²) CKD [34]. CKD participants had at least a 3-month history of stable kidney function ($\leq 10\%$ fluctuation in the eGFR) and had comorbid HTN with a stable antihypertensive medication regimen before enrollment. Exclusion criteria included severe CKD (eGFR <30 mL min⁻¹ 1.73 m⁻²); diabetes; HIV infection; heart failure; history of past coronary artery, cerebrovascular, aortic, or peripheral artery disease; symptomatic heart disease determined by electrocardiogram, stress test, and/or history; hepatic enzyme concentrations >2 times the upper limit of normal; severe anemia with a hemoglobin level <10 g/dL; history of nephrolithiasis; any serious systemic disease that might influence survival; current treatment with clonidine; clinical BP >160/90 mm Hg or <110/60; change in medications or surgery within the past 3 months; and drug or alcohol use disorders.

Study Design

After written informed consent was obtained, office BP, basic metabolic panel, and urinary albumin-to-creatinine ratio levels were obtained during a screening visit. During a separate visit, brachial artery flow-mediated dilation (FMD) was measured before maximal exercise testing. Muscle sympathetic nervous activity (MSNA) was obtained by microneurography during a separate visit. All measurements were obtained in a quiet, temperate (21°C) environment, after abstaining from food, caffeine, smoking, and alcohol for at least 12 h, and exercise for at least 24 h. A standard snack of 2 Graham crackers and one small boxed juice was given after the FMD measurements and just before the exercise treadmill test. All participants reported having taken prescribed medications as normally directed. Patients with CKD were divided into dichotomous groups by RASi usage (either ACEi or ARB) at the time of the study visit.

Measurements and Procedures

Blood Pressure

Baseline BP was measured after 5 min of rest in a seated position with the arm supported at the heart level using an appropriately sized cuff per American College of Cardiology/American Heart Association (ACC/AHA) guidelines [35] with an automated device (Omron, HEM-907XL; Omron Healthcare, Kyoto, Japan). The mean arterial BPs were calculated as $2/3$ diastolic BP (DBP) + $1/3$ systolic BP (SBP). Throughout the exercise treadmill test, BP was measured manually by a single investigator (J.P.). The heart rate (HR) was monitored using continuous ECG during the exercise treadmill test.

Maximal Exercise Treadmill Test

Participants underwent a modified Balke protocol, as previously described [5]. Briefly, participants were allowed to warm up for 2 min on a treadmill (GE T2100 controlled via GE Case V6.5 software) set to a speed of 1.5 mph with the slope set to 0%. At the start of the test, the speed was increased to 2.0 mph. At 3 min, and every subsequent 3 min, the treadmill slope was increased by 3.5%. At the 18th minute, the speed was increased to 3.0 mph, while the treadmill slope was decreased to 12.5%. The slope was again increased by 3.5% every 3 min until the participant achieved exhaustion. The HR was monitored continuously with ECG. BP was manually measured by the same investigator at 2 min and 30 s into each stage; the rate of perceived exertion was reported at 2 min and 50 s into each stage. Expired O_2 , CO_2 , and ventilation were recorded every 30 s (Sensormedics VMax Spectra 29) during exercise to determine exercise capacity (peak oxygen consumption [VO_{2peak}]). The VO_{2peak} was defined as the highest VO_2 observed during maximal exercise testing.

Muscle Sympathetic Nerve Activity

Microneurography was performed to record multiunit postganglionic MSNA directly from the peroneal nerve, as previously described [36]. A tungsten microelectrode (tip diameter 5–15 μm) (Bioengineering, University of Iowa) was inserted into the peroneal nerve, and a reference microelectrode was inserted subcutaneously 1–2 cm from the recording electrode while the participants were in the supine position. The signals were amplified (total gain: 50,000–100,000), filtered (700–2,000 Hz), rectified, and integrated (time constant 0.1 s) to obtain a mean voltage display of sympathetic nerve activity (Nerve Traffic Analyzer, model 662C-4; University of Iowa, Bioengineering) that was recorded by the LabChart 7 Program (PowerLab 16sp; ADInstruments). Continuous ECG was recorded simultaneously with the neurogram using a BioAmp System. Beat-to-beat arterial BP was measured via finger photoplethysmography [37]. Absolute values of BP were internally calibrated using a concomitant upper arm BP reading and were calibrated at the start and every 15 min throughout the study. The tungsten microelectrode was manipulated to obtain a satisfactory nerve recording that met previously established criteria [38]. After 10 min of rest, baseline BP, HR, respiratory rate, and MSNA were recorded continuously for 10 min.

Brachial Artery FMD

A forearm occlusion cuff was placed on participants while they were in a supine position. A 13-MHz high-resolution ultrasound transducer (Acuson Aspen) was placed longitudinally 2–10 cm above the antecubital fossa to record brachial artery measurements.

Baseline values were obtained by averaging the diameter and blood velocity over 3 cardiac cycles measured via ECG gating to capture end-diastolic arterial diameters. The forearm cuff was inflated to suprasystolic levels (50 mm Hg above SBP) using a rapid cuff inflator (D.E. Hokanson) for 5 min. The peak hyperemic blood velocity was measured by Doppler ultrasound during the first 10 s following cuff release. Diameter measurements were obtained 60 and 90 s following cuff release. FMD calculations were made using 60-s and 90-s measurements to determine the peak diameter. Arterial diameters were measured and analyzed by a single investigator blinded to clinical status of the participant from digitized images utilizing customized software (Medical Imaging Applications). FMD is given as the per cent change in the artery diameter from baseline: (peak hyperemic diameter – baseline diameter)/baseline diameter. The shear rate at baseline and peak hyperemia was calculated as $4 \times$ peak blood velocity/arterial diameter. FMD values were then normalized for the peak hyperemic shear rate. This calculation of the shear rate is consistent with our previous reports [39].

Data Analysis

Muscle Sympathetic Nerve Activity

MSNA and ECG data were exported and analyzed offline via specialized software (WinCPRS; Absolute Aliens, Turku, Finland). R-waves were detected and marked from the continuous ECG recording. MSNA bursts were automatically detected by the program using the following criteria: 3:1 burst-to-noise ratio within a 0.5-s search window, with an average latency in burst occurrence of 1.2–1.4 s from the previous R-wave. After automatic detection, the ECG and MSNA neurograms were visually inspected for accuracy of detection by a single investigator (J. Park). MSNA was expressed as the burst frequency (bursts/min) and burst incidence (bursts/100 heartbeats).

Statistics

Values are presented as mean $\pm$ standard deviation unless otherwise noted. Participant characteristics and primary outcomes (VO_{2peak} , MSNA, and FMD) between RASi users and non-RASi users in CKD patients were compared between groups via independent t tests for continuous variables, χ^2 tests for categorical variables, and ANOVA for adjusted comparison analysis with VO_{2peak} in exercise hemodynamic variables. The comparison between CKD and CON groups were also performed via independent t tests. The Pearson correlation test was performed to examine the linear relationship between VO_{2peak} and MSNA and FMD in CKD patients. Multivariable linear regression was used to describe the predictability of MSNA and FMD combined with and without RASi usage on VO_{2peak} in CKD patients. An $\alpha < 0.05$ was considered statistically significant for all analyses. All analyses were performed using SPSS version 26.0 (IBM Corporation, Somers, NY, USA).

Results

Participant Characteristics

A total of 55 participants including patients with CKD ($n = 35$) and age-matched CONs without CKD ($n = 20$) completed the study. The CKD group was further divided by RASi usage: CKD no RASi ($N = 10$) and CKD + RASi

Table 1. Participant characteristics

Characteristics	CKD no RASi (n = 10)	CKD + RASi (n = 25)	p value [#]	CON (n = 20)	p value ^{&}
Age, years	56.6±6.3	56.8±7.4	0.911	52.5±8.2	0.065
Sex (male), n (%)	10 (100)	25 (100)	0.226	21 (95)	0.375
Race, n (%)					
Black	10 (100)	23 (92)	0.504	19 (86)	0.248
White	0	2 (8)		3 (14)	
Height, cm	180.0±4.9	180.8±7.0	0.787	179.7±6.4	0.724
BMI, kg/m ²	26.0±14.2	32.6±8.0	0.095	28.8±4.5	0.422
HTN, n (%)	10 (100)	25 (100)		12 (60)	0.000
Antihypertensive medications, n (%)					
ACEi/ARB	0	17/8 (100)	1.000	3 (17)	0.002
CCB	7 (70)	14 (56)	0.458	6 (27)	0.015
Diuretics	3 (30)	11 (44)	0.698	9 (41)	0.598
β-Blockers	5 (50)	7 (28)	0.380	1 (5)	0.001
Aldosterone receptor blockers	3 (30)	0	0.015	1 (13)	0.653
α-Blockers	0	4 (16)	0.554	1 (13)	0.519
Hydralazine statin	3 (30)	0	0.020	0	0.271
eGFR, mL min ⁻¹ 1.73 m ⁻²	51.4±19.1	48.3±10.8	0.540	89.5±12.6	0.000
UACR, mg/g	93±122	147±236	0.629	1±0	0.006

Values are expressed as means ± SD. RASi, renin-angiotensin system inhibitors; CKD, chronic kidney disease; CONs, controls; BMI, body mass index; CCB, calcium channel blocker; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; HTN, hypertension; SD, standard deviation. [#]Indicates group comparison by RASi usage in CKD patients. [&]Indicates group comparison between all CKD patients versus CON participants.

Table 2. Exercise hemodynamic parameters in CKD patients with and without RASi and CONs

Hemodynamics	CKD no RASi (n = 7)	CKD + RASi (n = 18)	p value [#]	CON (n = 20)	p value ^{&}
SBP pre, mm Hg	137±9	132±14	0.329	124±13	0.018
DBP pre, mm Hg	84±4	84±10	0.853	75±9	0.003
MAP pre, mm Hg	102±5	99±10	0.543	91±9	0.002
HR pre, bpm	63±11	64±12	0.965	67±15	0.332
SBP max, mm Hg	174±27	191±28	0.181	183±23	0.719
DBP max, mm Hg	88±5	89±12	0.764	84±10	0.118
MAP max, mm Hg	115±11	121±15	0.374	114±14	0.232
HR max, bpm	114±25	139±25	0.033	150±17	0.012
SBP 4 min-post, mm Hg	136±5	133±13	0.611	130±16	0.540
DBP 4 min-post, mm Hg	85±6	80±9	0.261	74±13	0.036
MAP 4 min-post, mm Hg	102±4	98±9	0.284	93±11	0.053
HR 4 min-post, bpm	76±5	90±18	0.108	96±15	0.066

Values are expressed as mean±SD. Significant p values are shown in bold. RASi, renin-angiotensin system inhibitors; CKD, chronic kidney disease; CONs, controls; HEA, healthy control; VO_{2peak}, peak oxygen consumption; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; HR, heart rate; pre, measurement obtained just prior to the start of the exercise; max, the maximal value obtained during the exercise; 4 min-post, measurement obtained 4 min after exercise cessation; SD, standard deviation. [#]Indicates group comparison by RASi usage in CKD patients. [&]Indicates group comparison between all CKD patients versus CON participants.

Fig. 1. VO_{2peak} (A), exercise duration in the maximal treadmill test (B), MSNA (C), and FMD (D) in CKD patients treated with RASi (CKD + RASi) and without RASi (CKD no RASi) and CONs without CKD. *Indicates a significant difference ($p < 0.05$) from the CKD no RASi group. #Indicates a significant difference ($p < 0.05$)

from the CKD + RASi group. CKD, chronic kidney disease; RASi, renin-angiotensin system inhibitor; MSNA, muscle sympathetic nervous activity; FMD, flow-mediated dilation; CON, control; VO_{2peak}, peak oxygen consumption.

($N = 25$). Participant characteristics are shown in Table 1. The majority of participants in all groups were Black males. In patients with CKD, the main causes of CKD were HTN ($n = 14$), an unknown cause combined with HTN ($n = 8$), polycystic kidney disease ($n = 2$), glomerulonephritis ($n = 1$), and unknown ($n = 10$). All participants with CKD and 60% of CONs had HTN. None of the participants had comorbid diabetes (exclusion criterion). There were no significant differences in demographics, anthropometric characteristics, antihypertensive medication, eGFR, urinary albumin-to-creatinine ratio, or HMG CoA reductase inhibitors (statins) use between CKD no RASi and CKD + RASi. Compared to CONs,

CKD patients as a whole had greater proportion of hypertensives and higher rates of antihypertensive medication usage (calcium channel blocker, RASi, and β -blockers) ($p < 0.05$ for all).

Exercise Hemodynamics in CKD Patients with and without RASi Treatment

Hemodynamics before (pre), during (max), and after (post) maximal treadmill exercise testing for all groups are shown in Table 2. There was no difference in hemodynamic measures at pre- and postexercise between CKD no RASi and CKD + RASi. Compared to CKD groups, CONs had lower SBP, DBP, and mean arterial BP but not

Fig. 2. Association between VO_{2peak} and FMD (**A**) and MSNA (**B**) in patients with CKD. Closed circles (•) for CKD patients with RASi and open circles (O) for CKD patients without RASi. CKD, chronic kidney disease; RASi, renin-angiotensin system inhibitor; MSNA, muscle sympathetic nervous activity; FMD, flow-mediated dilation; VO_{2peak} , peak oxygen consumption.

HR at pre-exercise, lower DBP at postexercise, and higher max HR during exercise. CKD + RASi had a greater max HR during maximal treadmill exercise than CKD no RASi, which was no longer significant after adjusting for VO_{2peak} levels or exercise duration ($p > 0.05$ for all).

Exercise Capacity, Sympathetic Nervous Activity, and Endothelial Function in CKD Patients with and without RASi Treatment

CKD + RASi had higher VO_{2peak} than CKD no RASi but lower VO_{2peak} than CONs (23.3 ± 5.8 vs. 16.4 ± 2.9 mL/min/kg; $p = 0.007$, vs. 30.0 ± 7.7 ; $p = 0.016$ mL/min/

kg, respectively; Fig. 1A), suggesting that RASi use is associated with higher exercise capacity in CKD but is not associated with restoration of exercise capacity to the level of CONs. CKD + RASi had longer exercise duration during maximal treadmill exercise testing than sCKD no RASi, while there was no difference in exercise duration between CKD + RASi and CONs (17 ± 5 vs. 12 ± 5 min; $p = 0.005$, vs. 22 ± 7 min; $p = 0.819$, respectively; Fig. 1B), suggesting that RASi use is associated with increased endurance in CKD to the level of CONs.

CKD + RASi had lower resting MSNA than CKD no RASi but similar resting MSNA levels compared to CONs (43.9 ± 7.1 vs. 53.8 ± 8.2 bursts/min; $p = 0.009$, vs. 38.0 ± 20.3 bursts/min; $p = 0.103$, respectively; Fig. 1C), suggesting that RASi use is associated with sympathoinhibition in CKD to the level of CONs. CKD + RASi had higher brachial artery FMD than CKD no RASi but lower FMD than CONs (3.2 ± 2.6 vs. $1.3 \pm 1.6\%$; $p = 0.007$, vs. $5.0 \pm 3.0\%$; $p = 0.045\%$, respectively; Fig. 1D), suggesting that RASi use is associated with higher NO-mediated endothelial function in CKD but is not associated with restoration of endothelial function to the level of CONs.

Predictors of Exercise Capacity in CKD Patients

VO_{2peak} was positively associated with FMD ($r = 0.417$, $p = 0.038$) but was not associated with resting MSNA ($r = -0.296$, $p = 0.219$) in CKD patients (Fig. 2A, B, respectively). Multivariable linear regression analysis demonstrated that both FMD alone and combined with RASi usage status significantly predicts VO_{2peak} in CKD patients (Table 3, Model 1, 2). Although MSNA alone was not predictive, the combination of MSNA and RASi usage significantly predicts VO_{2peak} in CKD patients (Table 3, Model 3, 4). When FMD, MSNA, and RASi were considered together as potential predictors, there was a trend toward predicting VO_{2peak} in CKD patients (Table 3, Model 5).

Discussion

The present study demonstrates that CKD patients on RASi have higher exercise capacity than a similar cohort of CKD patients not on RASi. Greater exercise capacity in RASi-treated group was associated with lower resting SNS activity and higher NO-dependent vascular endothelial function in patients with CKD. These findings support our hypothesis that the RASi is associated with improved exercise capacity in CKD, and these effects may

Table 3. Multivariable regression analysis with MSNA, FMD, and RASi usage for VO_{2peak} in CKD patients

Model	Dependent variable	Predictor	Unstandardized β	Standardized β	R^2	Adj R^2	Model p value
1	VO _{2peak}	FMD	0.919	0.414	0.174	0.138	0.038
2	VO _{2peak}	FMD RASi	0.609 5.696	0.276 0.436	0.344	0.284	0.010
3	VO _{2peak}	MSNA	−0.181	−0.296	0.088	0.034	0.219
4	VO _{2peak}	MSNA RASi	−0.011 6.762	−0.018 0.566	0.575	0.247	0.040
5	VO _{2peak}	FMD MSNA RASi	0.535 0.104 6.672	0.293 0.170 0.558	0.379	0.255	0.061

Significant p values are shown in bold. MSNA, muscle sympathetic nervous activity; FMD, flow-mediated dilation; RASi, renin-angiotensin system inhibitors; VO_{2peak}, peak oxygen consumption; CKD, chronic kidney disease.

be mediated by via differences in SNS activity and NO-dependent endothelial function.

Exercise intolerance is a clinical hallmark of CKD that begins in the early stages of CKD [1]. Reduced exercise capacity is an independent predictor of the development and progression of CKD [6, 7] and is associated with increased risk of hospitalization and mortality [3–5]. This impairment in physical performance may also result in a reduction in exercise capacity as well as an inability to perform activities of daily living, therefore negatively affecting quality of life in patients with CKD [8]. The mechanisms of exercise intolerance in CKD are complex, involving central and peripheral abnormalities that limit efficient oxygen delivery and utilization during exercise [9–11]. The present study adds novel evidence that pharmacological inhibition of the RAS is associated with beneficial effects on exercise capacity in patients with CKD. Previous studies suggest that RAS blockade may prevent or restore declines in physical functioning in populations with low physical functioning including older adults [40] and patients with heart failure [23, 24]. ACEi treatment was associated with an attenuated age-related reduction in the walking speed and muscle strength in 641 hypertensive elderly women over the course of 3 years [20]. Moreover, a randomized controlled trial demonstrated that ACEi treatment improved physical function in functionally impaired elderly individuals, and the degree of improvement was equivalent to that reported after 6 months of exercise training [21]. Likewise, ARB treatment also showed an improvement in physical function in the elderly [22], peripheral artery disease [25], and in

animal models [18] and patients with heart failure [23, 24]. Conversely, other studies [41–44] have reported no association between RASi use and indicators of physical function in functionally impaired populations. Self-reported incidence of frailty was similar between ACEi users and nonusers regardless of the duration of ACEi usage in older women [44]. RASi use failed to improve exercise capacity in older adults with high CV risk [41] and individuals with myocardial hypertrophy [43] and right-ventricular dysfunction [42]. These mixed results suggest that the interaction between RASi and exercise performance cannot be generalized in heterogeneous populations characterized by exercise intolerance, likely due to different origins of physical functional impairment (central cardiac, peripheral limitations, or a mixture of both) and different mechanisms of population-specific RASi-driven health benefits.

We observed a positive effect of RASi on exercise capacity in a population of predominantly Black males with mild-to-moderate CKD. The mechanisms by which RAS inhibition may modulate physical functioning remain poorly understood. RASi are widely used in the treatment of HTN and CV diseases due to their BP-lowering effects and end-organ protection [14–16]. In CKD, RASi treatment has been shown to exert reno-protective and antiproteinuric effects beyond their well-known antihypertensive effects and is thus recommended as a first-line antihypertensive agent in this population [17, 45]. However, not all CKD patients, particularly those without proteinuria, are necessarily treated with RASi since the greatest nephro-protective effects of RASi are noted in

patients with proteinuria [45]. The CV-protective effects of RASi are mediated primarily through inhibition of the production and activity of the main downstream effector angiotensin II (Ang II) and its interaction with angiotensin type 1 receptor (AT₁R) [46]. Inhibition of Ang II-AT₁R signaling either by ACEis or ARBs as well as suppression of the degradation of bradykinin by ACEis promotes NO production [29], leading to improved endothelial function [32, 33]. This improvement in endothelial function with a RASi and the resultant improvements in blood flow may therefore be associated with improvements in physical function by optimizing nutrient and oxygen supply to exercising skeletal muscle [47]. In this regard, improvement in insulin sensitivity, glycogen storage, and glucose uptake by skeletal muscles have been reported with RASi treatment, supporting a role in improved muscle metabolic efficiency [48]. Our results demonstrate that despite similar resting BP between CKD patients treated with RASi and those not treated with RASi, the RASi-treated group exhibited greater endothelial function, which was associated with increased exercise capacity in CKD. These results are consistent with previous findings that similarly report improvements in endothelial function following RASi treatment [32, 33].

Ang II is also known to enhance SNS activation both peripherally and centrally by facilitating presynaptic release of norepinephrine (NE) and inhibiting NE reuptake at sympathetic nerve terminals, enhancing the density of sympathetic innervation and binding to AT₁R in SNS control centers in the brain [27, 28]. CKD is characterized by chronically elevated SNS activity, and RASi treatment has been shown to reduce MSNA levels in patients with CKD [26, 31], suggesting a RAS-dependent sympathetic hyperactivity in CKD. Ang II-mediated increases in NE release could contribute to a reduction in physical capacity by impairing blood flow and oxygen delivery to exercising skeletal muscle. Attenuation of sympathetic vasoconstriction in exercising skeletal muscles, termed functional sympatholysis, is a protective physiological mechanism to ensure proper muscle perfusion to meet increased metabolic demands during exercise [49]. Functional sympatholysis has been shown to be impaired in patient populations characterized by exaggerated SNS activity such as HTN [50] and end-stage kidney disease patients [51]. Functional sympatholysis can be restored with ARBs but not with other classes of antihypertensives in patients with HTN [50, 52], suggesting an important role of RAS in sympathetically mediated vasoconstriction in exercising skeletal muscles. Although the underlying

mechanisms are unknown, our findings support the contention that RASi-mediated reduction in SNS activity may play a role in improved exercise capacity in CKD since hypertensive CKD patients on a RASi had a lower resting MSNA level, which was in turn associated with and predictive of increased exercise capacity in multivariate analyses. Interestingly, the predictability of MSNA for exercise capacity was enhanced when RASi usage was considered as a co-predictor suggesting a potential synergic effect of SNS and RAS inhibition in preserving exercise capacity in CKD. However, care should be taken in the interpretation of these cross-sectional analyses, and future long-term studies are needed to examine the effects of RASi treatment on sympathetic vasoconstriction and its potential contribution to exercise capacity in patients with CKD.

Limitations

This study was an observational study; therefore, the causal relationship between RASi usage, exercise capacity, SNS activity, and endothelial function cannot be determined in this cross-sectional study. This study is also limited by a small sample size, and longitudinal studies with larger sample sizes are needed to fully ascertain these findings of relationship between RAS blockade, SNS activity, and endothelial function. Only males were enrolled, and thus, the present findings may not be generalizable to females. Furthermore, only mild-to-moderate CKD (stages II and III) were included; therefore, the results may not be generalizable to more severe CKD (stage IV) or end-stage kidney disease. The RASi group combined patients who were on either ACEis or ARBs and was not powered to detect differences between ACEi and ARB subgroups. The dosage and duration of RASi administration and other concomitant vasoactive and chronotropic medications were not controlled; however, there was no significant difference in antihypertensive medication usage between groups with and without RASi. Functional sympatholysis was not measured, so it is unclear if reductions in SNS activity improve exercise capacity in CKD by improving muscle perfusion.

Conclusion

Our results indicate that hypertensive CKD patients treated with a RASi have higher exercise capacity that is associated with lower SNS activity and higher endothelial function. These findings provide novel insights on the

potential beneficial effects of RAS blockade on physical function in CKD and the potential mechanistic roles of SNS activity and endothelial function on RAS-mediated preservation of exercise capacity, although care should be taken with the interpretation due to the small sample size and the cross-sectional design of the study. Long-term randomized trials with a larger sample size are needed to examine causal links between RASi treatment and physical function in CKD, as well as the underlying autonomic and vascular mechanisms.

Statement of Ethics

This study was conducted ethically in accordance with World Medical Association Declaration of Helsinki. This study was approved by the Emory University Institutional Review Board and the Atlanta VA Healthcare System Research and Development Committee (IRB00019181). Written informed consent was obtained from all participants to participate in the study.

Conflict of Interest Statement

No conflicts of interest, financial or otherwise, are declared by the author(s).

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Author Contributions

J.H.J. and J.P. conceived and designed the research; D.D., A.A.Q., and J.P. performed the experiments; J.H.J., J.D.S., and J.P. analyzed the data; J.H.J., J.D.S., A.A.Q., and J.P. interpreted the results of the experiments; J.H.J. and J.P. prepared the figures; J.H.J. and J.P. drafted the manuscript; J.H.J., J.D.S., A.A.Q., D.D., and J.P. edited and revised the manuscript; J.H.J., J.D.S., A.A.Q., D.D., and J.P. approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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