Exercise pressor reflex in humans with end-stage renal disease

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Park J, Campese VM, Middlekauff HR. Exercise pressor reflex in humans with end-stage renal disease. Am J Physiol Regul Integr Comp Physiol 295: R1188–R1194, 2008. First published August 6, 2008; doi:10.1152/ajpregu.90473.2008.—Previous work has suggested that end-stage renal disease (ESRD) patients may have an exaggerated sympathetic nervous system (SNS) response during exercise. We hypothesized that ESRD patients have an exaggerated blood pressure (BP) response during moderate static handgrip exercise (SHG 30%) and that the exaggerated BP response is mediated by SNS overactivation, characterized by augmented mechanoreceptor activation and blunted metaboreceptor control, as has been described in other chronic diseases. We measured hemodynamics and muscle sympathetic nerve activity (MSNA) in 13 ESRD and 16 controls during: 1) passive hand movement (PHM; mechanoreceptor isolation); 2) low-level rhythmic handgrip exercise (RHG 20%; central command and mechanoreceptor activation); 3) SHG 30%, followed by posthandgrip circulatory arrest (PHGCA; metaboreceptor activation); and 4) cold pressor test (CPT; nonexercise stimulus). ESRD patients had exaggerated increases in systolic BP during SHG 30%; however, the absolute and relative increase in MSNA was not augmented, excluding SNS overactivation as the cause of the exaggerated BP response. Increase in MSNA was not exaggerated during RHG 20% and PHM, demonstrating that mechanoreceptor activation is not heightened in ESRD. During PHGCA, MSNA remained elevated in controls but decreased rapidly to baseline levels in ESRD, indicative of markedly blunted metaboreceptor control of MSNA. MSNA response to CPT was virtually identical in ESRD and controls, excluding a generalized sympathetically hyporeactive in ESRD. In conclusion, ESRD patients have an exaggerated increase in MSNA during SHG 30% that is not mediated by overactivation of the SNS directed to muscle. SBP responses were also exaggerated during mechanoreceptor activation and metaboreceptor activation, but without concomitant augmentation in MSNA responses. Metaboreceptor control of MSNA was blunted in ESRD, but the overall ability to mount a SNS response was not impaired. Other mechanisms besides SNS overactivation, such as impaired vasodilatation, should be explored to explain the exaggerated exercise pressor reflex in ESRD.

blood pressure; muscle sympathetic nerve activity; hemodialysis; metaboreceptor

PATIENTS WITH END-STAGE RENAL disease (ESRD) suffer from profound exercise intolerance, the mechanisms of which are not fully understood. The potential role of abnormal hemodynamic and autonomic responses during exercise as contributors to exercise intolerance in ESRD has been largely unexplored. Prior studies have observed that ESRD patients have greater increases in norepinephrine levels during exercise compared with controls (4, 7, 13), although this is not a universal finding (6), and total peripheral resistance during exercise was found to be significantly higher in a group of pediatric renal transplant recipients (19). If ESRD patients do have an augmented blood pressure elevation mediated by an exaggerated sympathetic nervous system (SNS) response during exercise, then such neurovascular abnormalities could potentially contribute to exercise impairment by increasing cardiac workload during exercise.

The normal physiological responses during exercise include an increase in blood pressure, heart rate (HR), and SNS activity that serve to meet the increased metabolic demand of skeletal muscle during exercise (12, 28). SNS activation during exercise is mediated by two main control mechanisms: 1) central command, which refers to a signal arising from within the central nervous system that is linked to the perceived effort of exercise, and is important in increasing SNS outflow only at maximal or near-maximal effort; and 2) the exercise pressor reflex, mediated by sensory nerve endings within the skeletal muscle that, when stimulated during exercise, result in a reflex activation of central sympathetic outflow (12, 26). These sensory nerve endings include the metaboreceptors that are sensitized by ischemic metabolites generated during exercise and mechanoreceptors that are largely activated by mechanical stretch. In healthy humans, the muscle mechanoreceptors are paramount in generating the reflex increases in SNS activity during static exercise (16). However, patients with chronic heart failure (CHF), another disease state characterized by baseline SNS overactivity and exercise intolerance, manifest abnormalities of the exercise pressor reflex characterized by a blunted metaboreceptor activation of SNS activity during exercise (29) and an exaggerated reflex activation of SNS activity mediated by the mechanoreceptors (20, 21).

The exercise pressor reflex has not yet been studied in ESRD patients and may be one component in the pathogenesis of exercise dysfunction, given the role of sympathetic activation on blood flow regulation and total peripheral resistance during exercise. Furthermore, whether abnormal blood pressure responses occur during exercise in ESRD remains controversial, and SNS activity assessed by plasma norepinephrine levels during exercise have shown mixed results, whereas real-time recordings of muscle sympathetic nerve activity (MSNA) by microneurography during exercise in ESRD have not previously been performed. The hypotheses tested in this study were 1) ESRD patients have exaggerated increases in blood pressure and HR during short-term moderate static handgrip exercise (SHG 30%); 2) the exaggerated increases in blood pressure are mediated by augmented increases in SNS activity; and 3) augmented SNS activity during exercise is due to abnormal regulation of the exercise pressor reflex, with exaggerated mechanoreceptor activation and blunted metaboreceptor activation of SNS activity.
METHODS

Study Population

The study population consisted of 29 total participants (age range 21–59 yr): 13 ESRD patients, and 16 healthy, age-matched controls. Exclusion criteria for all participants included smoking, illicit drug use, and major comorbid conditions, including diabetes, nephropathy, vascular disease, uncontrolled anemia, or any clinical evidence of heart disease determined by electrocardiogram (ECG), echocardiogram, stress test, and/or history. Two out of 16 controls and 4 out of 13 ESRD patients had hypertension that was controlled on an average of 2.5 medications. One hypertensive control participant was being treated with an ANG II receptor blocker, and the other was diet-controlled. The four hypertensive ESRD patients were being treated with ANG II receptor blocker (2), dihydropyridine calcium channel blocker (4), β-blocker (2), and β-blocker with α-blocking activity (2). Antihypertensive medications were held on the day of the study. All ESRD patients were on chronic maintenance hemodialysis at a frequency of three times per week, for ~3.5 h each session. All ESRD patients were being treated with erythropoiesis stimulating agents, and time on dialysis ranged from <1 mo to 14 yr, with an average duration of 2.4 yr. The etiology of ESRD was autosomal dominant polycystic kidney disease (2), hypertension (1), shock (1), lithium toxicity (1), chronic glomerulonephritis (1), and unknown (7). The University of Southern California Institutional Review Board approved the study protocol, and a written informed consent was obtained from each participant.

MEASUREMENTS AND PROCEDURES

Blood pressure. Arterial blood pressure was measured with an automated sphygmomanometer (Dinamap PRO Series) intermittently every 20 min throughout the experimental protocol and during the last minute of each exercise maneuver. Baseline measures were obtained while the participant was seated, after 5 min of quiet rest. The arm was supported at heart level, and an appropriately sized blood pressure cuff with bladder encircling at least 80% of the upper arm was used. Each data point of blood pressure was the mean of at least three consecutive readings.

MSNA. Multiunit postganglionic sympathetic nerve activity directed to muscle (MSNA) was recorded directly from the peroneal nerve by microneurography, as previously described (32, 36). A tungsten microelectrode (tip diameter 5–15 μm) was inserted in the nerve, and a reference microelectrode was inserted subcutaneously 1–2 cm from the recording electrode. 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 that was recorded by the Chart 5 Program (PowerLab 16sp; ADInstruments). Lead II of the ECG was recorded simultaneously with the neurogram. All MSNA recordings met previously established criteria (8, 9, 15). Sympathetic bursts were identified by visual inspection of nerve bursts by a single investigator without knowledge of the participant’s status as control or patient. MSNA was expressed as burst frequency (bursts/min), bursts per 100 heart beats, and total activity (arbitrary units/min). Total activity was calculated by measuring the amplitude of each identified burst in arbitrary units during each minute of intervention or rest (i.e., mean burst amplitude multiplied by burst frequency).

SHG 30%. SHG 30% elicits an increase in MSNA (16) by activating metaboreceptors, mechanoreceptors, and central command. The participant was asked to squeeze a hand dynamometer (Stoelting) with maximal force. The highest force attained from three attempts was considered the maximum voluntary contraction (MVC). SHG 30% was performed by squeezing the hand dynamometer at 30% of MVC in a sustained manner for 3 min. The participant was instructed to avoid inadvertent Valsalva and to maintain normal breathing patterns.

Posthandgrip circulatory arrest. Posthandgrip circulatory arrest (PHCA) was performed immediately after SHG 30%, and traps ischemic metabolites within the forearm and thereby isolates muscle metaboreceptors from mechanoreceptors and central command. Before the end of the 3-min SHG exercise (5 s), an upper arm blood pressure cuff was inflated to suprasystolic levels (220 mmHg) proximal to the exercising forearm for 2 min to trap the metabolites within the forearm. The participant remained relaxed during this maneuver, eliminating any contribution from mechanoreceptors or central command.

Passive hand movement. During this passive hand movement (PHM), the participant remained passive, thereby isolating muscle mechanoreceptors from central command and mechanoreceptors. The participant’s wrist was flexed and extended by the investigator at a rate of 1 flexion/2 s. A metronome was used to optimize uniformity of contraction rate.

Rhythmic handgrip exercise. Low-level rhythmic handgrip exercise (RHG 20%) engages muscle mechanoreceptors and central command, without engagement of muscle metaboreceptors (3). The participant squeezed the hand dynamometer intermittently at 20% MVC for 3 min, at a rate of 1 contraction/2 s.

Cold pressor test. This maneuver is known to elicit an increase in MSNA (33) and was performed to test whether ESRD patients had intact capacity to mount MSNA responses to a nonexercise stimulus or, instead, had a generalized inability to increase MSNA due to uremic neuropathy or maximally elevated baseline levels of MSNA. Cold pressor test (CPT) was performed by submerging the participant’s hand in cold water up to the wrist for 1 min. The temperature of the water was ~0–1°C. Participants were asked to grade the amount of pain experienced during the CPT on a scale of 1–5 (least to most severe) to ensure that ESRD patients and controls experienced the same amount of discomfort during the test.

Experimental Protocol

Figure 1 depicts the timeline of the experimental protocol. All participants were studied in the early afternoon, after abstaining from food for 4 h and exercise, caffeine, and alcohol for at least 12 h. All ESRD patients were studied on a nondialysis day. The study room was quiet, semidark, and temperate (~21°C). Participants were placed in a supine position and fitted with a blood pressure cuff on the upper arm for intermittent automatic blood pressure monitoring and ECG patch electrodes for continuous HR recordings. The leg was positioned for microneurography, and the tungsten microelectrode was...
inserted and manipulated to obtain a satisfactory nerve recording. After 10 min of rest, baseline blood pressure and HR were measured, and baseline MSNA was recorded for 10 min. Participants then performed the following maneuvers in random order: 1) RHG 20% for 3 min; 2) SHG 30% for 3 min, followed by 2 min of PHGCA; 3) PHM for 3 min; and 4) CPT for 1 min. A subset of the study population underwent CPT (13 controls, 8 ESRD). Baseline characteristics and responses to all interventions among the subgroups that underwent CPT were similar to that of the whole ESRD and control cohorts. Recovery time (40 min) was given between each maneuver, allowing sufficient time for blood pressure, HR, and MSNA to return to baseline levels before each new intervention. Each exercise task was performed in the dominant arm, except in the case of an ESRD patient with an arteriovenous dialysis access in place in the dominant arm (n = 1). MSNA and HR were recorded continuously, and blood pressure was monitored intermittently throughout the protocol.

Data Analysis

Statistical analysis was performed using the SAS program (SAS Institutes). Baseline characteristics were compared using independent two-tailed t-tests. Two-way ANOVA with repeated measures was performed using PROC GLM to determine differences between groups (ESRD patients vs. controls) with respect to percent change from baseline in MSNA, systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR with time during each intervention: static handgrip, rhythmic handgrip, PHM, PHGCA, and CPT. When the overall F-test was significant, the contrast option for post hoc analysis was used to compare the groups for change from baseline for each time point. The possible confounding effects of age on study findings were investigated by: 1) performing linear regression of baseline MSNA levels on age for each group separately; 2) examining the correlation between age and percent change from baseline in MSNA at various time points; and 3) including age as a covariate in the repeated-measures analysis. Results were expressed as means ± SE. A P value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Controls and ESRD patients were well-matched for age, gender, and body mass index (P > 0.05) (Table 1). SBP was significantly higher at baseline in ESRD patients vs. controls (36.9 ± 4.4 yr) compared with controls (30.6 ± 1.0 yr) (P = 0.18). Linear regression analysis revealed the following relationship between age and MSNA: in the control group, MSNA = -402.94 + 48.72 × age ($r^2 = 0.14$, $P = 0.18$), and in the ESRD group, MSNA = 87.77 + 37.77 × age ($r^2 = 0.54$, $P = 0.0067$). However, there was no significant difference in correlation coefficients describing the relationship between age and MSNA between the ESRD and control groups ($P > 0.05$).

There was no significant difference in mean age between the ESRD group (36.9 ± 4.4 yr) and controls (30.6 ± 1.0 yr) ($P = 0.0091$) in ESRD patients (36.4 ± 3.3 bursts/min) compared with controls (25.6 ± 2.2 bursts/min). Similar results were obtained when MSNA was analyzed as bursts/100 heart beats.

Table 1. Baseline demographics, hemodynamics, and sympathetic activity

<table>
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<th>Control</th>
<th>ESRD</th>
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<td>n</td>
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<td>13</td>
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<td>Age, yr</td>
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<td>Gender (M/F)</td>
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<td>Systolic BP, mmHg</td>
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</table>

Data are expressed as means ± SE; n, no. of subjects. ESRD, end-stage renal disease; M, males; F, females; BP, blood pressure; MSNA, muscle sympathetic nerve activity. Baseline measurements in control participants and ESRD patients. *P < 0.05.

SHG 30%

During 3 min of SHG 30% MVC, there was a significantly greater percent increase in SBP from baseline levels in ESRD patients (+25.7 ± 4.0%) when compared with controls (+17.2 ± 1.7%, $P = 0.036$) (Fig. 2). DBP and HR responses were similar between the two groups. MSNA increased from baseline levels in both ESRD patients and controls during each minute of SHG (Fig. 3). The percent increase in MSNA from baseline during each minute of SHG 30% was lower in ESRD patients compared with controls when MSNA was quantitated as burst frequency (bursts/min) (Fig. 3A); however, this difference was eliminated when MSNA was quantitated as total activity (units/min), which takes into account both the burst amplitude and the frequency (Fig. 3B). The percent change in MSNA from baseline during SHG 30% was not significantly different between ESRD and controls when quantified as total activity in Fig. 3B ($P = 0.28$).

PHGCA (Muscle Metaboreceptor Isolation)

PHGCA was performed immediately after static exercise to isolate the muscle metaboreceptors from mechanoreceptors and central command. There was a significantly greater percent increase in SBP from resting baseline (measured before SHG 30%) during PHGCA in ESRD patients (+17.7 ± 2.1%) compared with controls (+11.6 ± 1.7%, $P = 0.038$) (Fig. 2). There were no significant differences in DBP and HR responses between the two groups ($P > 0.05$). The percent increase in MSNA from resting baseline levels (measured before SHG 30%) during each minute of PHGCA was significantly blunted in ESRD patients compared with controls ($P < 0.001$) (Fig. 3). MSNA remained elevated over resting baseline levels in controls (by an average of +62.0 ± 8.9% and +110.8 ± 16.3% in Fig. 3B), whereas MSNA decreased immediately toward resting baseline levels in ESRD patients (average change from baseline of +3.4 ± 5.2% in Fig. 3A and +6.4 ± 8.5% in Fig. 3B).

PHM (Muscle Mechanoreceptor Isolation)

PHM was performed for 3 min to isolate muscle mechanoreceptors from metaboreceptors and central command. During PHM, there was a trend toward greater SBP response in ESRD
patients (+2.8 ± 0.9%) compared with controls (−0.1 ± 1.0%, P = 0.056) (Fig. 2). There were no significant differences in DBP and HR responses between the two groups (P > 0.05). The change in MSNA during PHM was not significantly different between ESRD patients and controls (P = 0.42), and these results were similar when MSNA was analyzed as total activity (P = 0.92) (Fig. 4).

RHG 20% (Muscle Mechanoreceptor and Central Command Activation)

During 3 min of RHG at 20% MVC (RHG 20%), there was a significantly greater percent increase in SBP from baseline in ESRD patients (+8.4 ± 2.7%) compared with controls (+2.7 ± 0.9%, P = 0.024) (Fig. 2). There were no significant differences in DBP or HR response between the two groups (P > 0.05). The change in MSNA during RHG 20% was not significantly different between ESRD patients and controls (P = 0.32) (Fig. 5).

**CPT**

During 1 min of the CPT, SBP responses were not significantly different in ESRD (+19.9 ± 4.3% above baseline) compared with controls (+16.6 ± 2.3%) (P = 0.46) (Fig. 2). There were also no significant differences in HR responses between the two groups. However, there was a trend toward greater DBP response in controls (+22.0 ± 2.5%) compared with ESRD patients (+12.5 ± 4.8%) (P = 0.067). There was no significant difference in MSNA response during CPT in ESRD vs. controls (+85.9 ± 27.3% above baseline vs. 114.8 ± 31.8%, respectively, P = 0.56) (Fig. 6). ESRD patients were able to mount a similar increase in MSNA during CPT. The perception of pain during CPT on a five-point scoring system was the same between ESRD and controls (data not shown).
DISCUSSION

The major new findings of this study are that ESRD patients have 1) exaggerated increases in SBP during moderate SHG compared with controls; 2) exaggerated increases in SBP during metaboreceptor and mechanoreceptor activation; 3) equivalent increases in MSNA during SHG; 4) no augmentation of mechanoreceptor activation of MSNA; and 5) blunted metaboreflex activation of MSNA during exercise. These hemodynamic and neurovascular abnormalities of the exercise pressor reflex may contribute to the exercise intolerance of ESRD, which is a major feature of uremic myopathy (1, 5).

ESRD patients had augmented SBP responses during metaboreceptor isolation and low-level RHG during which mechanoreceptors and central command are activated. These exaggerated increases in SBP during exercise in ESRD appear to be specific to exercise and not to all sympathoexcitatory stimuli, since the SBP response to CPT was not augmented.

Fig. 4. Percent Change in MSNA during PHM. Percent change from baseline in MSNA during each minute of PHM. A: %change in MSNA quantitated as bursts/min. B: %percent change in MSNA quantitated as total activity in units/min. Values are expressed as means ± SE. The overall ANOVA F-test was nonsignificant (NS) (see RESULTS).

Fig. 5. Percent change in MSNA during rhythmic handgrip. Percent change in MSNA during each minute of RHG at 20% MVC (RHG 20%). A: %change in MSNA quantitated as bursts/min. B: %percent change in MSNA quantitated as total activity in units/min. Values are expressed as means ± SE. The overall ANOVA F-test was nonsignificant (see RESULTS).

Fig. 6. Percent change in MSNA during PHGCA and CPT. Percent change from resting baseline MSNA. ESRD indicates end-stage renal disease. *P < 0.05.
Interestingly, our results show that the exaggerated SBP response during exercise is not mediated by augmented mechanoreceptor activation of SNS outflow. This finding in ESRD is in contrast to the pathogenesis of exercise dysfunction in CHF in which increased mechanoreceptor stimulation explains the exaggerated exercise pressor reflex (20, 21). The major new finding of this study is that SNS overactivation in general does not appear to be the overriding mechanism underlying the augmented pressor response in ESRD, since MSNA responses during static exercise, rhythmic exercise, and passive exercise were all similar to controls. However, it is important to note that some degree of augmentation in mechanoreflex-mediated MSNA responses cannot be completely excluded because of the exaggerated pressor response during both passive and RHG in ESRD. Even in the presence of an exaggerated increase in SBP during passive and RHG in ESRD, the increase in MSNA was similar to that of controls during these maneuvers; therefore, controlling the augmented SBP response with nitroprusside administration might reveal exaggerated increases in mechanoreceptor-mediated MSNA response when baroreceptors are unloaded and should be tested in future studies.

However, SNS overactivation does not contribute to the exaggerated SBP response during mechanoreceptor isolation since we found that mechanoreceptor activation of MSNA was significantly blunted in ESRD. Muscle mechanoreceptors are activated by ischemic metabolites generated during exercise that signal to the brain the need to redirect blood flow from nonworking skeletal muscles and visceral tissues to exercising skeletal muscles (12, 14, 28). The mechanoreceptors are paramount in activating the MSNA response during static exercise in healthy humans (16) and serve in part to redirect blood flow from nonworking tissues to exercising skeletal muscle. Blunted mechanoreceptor activation of SNS activity may itself contribute to exercise dysfunction in ESRD by failing to correct the mismatch between muscle blood flow and metabolic needs. Blunted MSNA responses to mechanoreceptor activation have been described and implicated in the exercise dysfunction of other disease states such as heart failure (29), obesity (23, 31), essential hypertension (24), and ageing (17).

The mechanisms underlying blunted mechanoreceptor activation of MSNA in ESRD are unclear. Potential mechanisms might include failure to generate the ischemic metabolites that stimulate the mechanoreceptors, desensitization of group III and IV sensory afferent nerve endings within uremic muscle, and inhibitory control of neural sympathetic outflow from other afferent signals such as baroreceptors. ATP is one putative trigger of mechanoreceptor activation, and studies have shown that there is greater ATP depletion during exercise in ESRD (10, 30) because of impaired oxidative energy metabolism from limited muscle conductance (18, 22, 25, 30); therefore, reduced ATP availability may result in diminished mechanoreceptor activation. Because mechanoreceptors are blunted, and mechanoreceptors are not augmented in ESRD, an increased contribution of central command to MSNA activation during exercise could potentially explain the equivocal MSNA response during static exercise during which mechanoreceptors, mechanoreceptors, and central command are all engaged. MSNA control by central command can be tested by having the participant attempt an exercise task but rendered incapable of generating a muscle contraction by applying a neuromuscular blocking agent such as curare (34). The isolated contribution of central command to MSNA activation in ESRD was not tested in this study.

Blunted mechanoreceptor activation and the lack of an augmented MSNA response during static exercise are not due to a uremic neuropathy that renders ESRD patients incapable of mounting appropriate SNS responses nor due to higher baseline MSNA levels that result in an inability to further increase neural sympathetic discharge above an elevated or saturated baseline. Generalized neuropathy and maximized baseline levels are not likely, since we have shown that the absolute and relative increases in MSNA were preserved during SHG and during the CPT. Thus the SNS hyporeactivity to mechanoreceptor control is specific to exercise and not to all sympathoexcitatory stimuli, and the ability to augment central sympathetic outflow is preserved in ESRD.

Limitations

We recognize several limitations to our study. First, four ESRD patients and two control participants had hypertension controlled on medications or diet. Although we excluded most other comorbid conditions, including cardiovascular disease and diabetes, we were not able to exclude hypertensive dialysis patients, since the prevalence of hypertension among ESRD patients is quite high, upward of 85% in some reports (2). However, our results are likely not due to hypertension or antihypertensive medications, since our analysis revealed similar findings when data from the hypertensive participants were removed from both groups. In the same respect, because we studied healthy ESRD patients without comorbidities to isolate the effect of renal failure on the exercise pressor reflex, our study population may not be typical of the general dialysis population that more often has comorbid conditions of diabetes, heart failure, and vascular disease. Second, we recorded changes in SNS activity using microneurography and were therefore limited to measurements of sympathetic activity directed to muscle (MSNA). Total central SNS outflow or SNS activity directed to other organs were not measured; however, MSNA has been shown to correlate with whole body, cardiac, and renal norepinephrine spillover (35, 37). Third, we did not make measurements of forearm blood flow during these experiments. Rather, the focus of this study was on the reflex control of MSNA during exercise in ESRD. Whether abnormalities of blood flow to nonexercising and exercising skeletal muscle also occur in conjunction with our findings of blunted mechanoreflex control should be evaluated in future studies. In addition, since we found that an exaggerated MSNA response does not explain the exaggerated SBP response during exercise, other mechanisms such as alternative vasoconstrictors (e.g., endothelin-1) or impaired endothelium-mediated vasodilation during exercise in ESRD should be investigated. Alternatively, ESRD patients may have greater vascular reactivity to a given amount of norepinephrine, or a greater release of norepinephrine at sympathetic nerve endings per nerve discharge, such that similar or lesser MSNA responses could still result in a greater pressor response. These potential mechanisms should be tested in future studies.

Perspectives and Significance

Patients with ESRD have poor exercise tolerance and are at profoundly increased risk of cardiovascular disease and sudden...
death. In this study, we found that the SBP response to moderate SHG is augmented in ESRD patients without heart disease or neuropathy. Such an exaggerated pressor response during isometric exercise could predispose this population to exercise dysfunction and increased cardiovascular risk. The augmented SBP response persists during metaboreceptor and mechanoreceptor activation. The mechanisms underlying the exaggerated pressor response do not appear to include an augmentation in sympathetic nerve activity. In fact, we found that metaboreceptor activation of MSNA is blunted, although the capacity to generate sympathetic responses to other stimuli is preserved. Because heightened SNS activity during exercise does not explain the exaggerated pressor response, then other potential mechanisms such as impaired exercise-mediated vasodilatation, should be explored in future experiments.

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