Autonomic Neuroscience: Basic and Clinical 188 (2015) 74–81

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Abnormal neurocirculatory control during exercise in humans with chronic renal failure

Jeanie Park [a,b,*], Holly R. Middlekauff [c]

[a] Renal Division, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA
[b] Research Service Line, Department of Veterans Affairs Medical Center, Decatur, GA, USA
[c] Cardiology Division, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 16 May 2014
Received in revised form 13 September 2014
Accepted 13 October 2014

Keywords:
Exercise
Chronic renal failure
Sympathetic nerve activity

ABSTRACT

Abnormal neurocirculatory control during exercise is one important mechanism leading to exercise intolerance in patients with both end-stage renal disease (ESRD) and earlier stages of chronic kidney disease (CKD). This review will provide an overview of mechanisms underlying abnormal neurocirculatory and hemodynamic responses to exercise in patients with kidney disease. Recent studies have shown that ESRD and CKD patients have an exaggerated increase in blood pressure (BP) during both isometric and rhythmic exercise. Subsequent studies examining the role of the exercise pressor reflex in the augmented pressor response revealed that muscle sympathetic nerve activity (MSNA) was not augmented during exercise in these patients, and metaboreflex-mediated increases in MSNA were blunted, while mechanoreflex-mediated increases were preserved under basal conditions. However, normalizing the augmented BP response during exercise via infusion of nitroprusside (NTP), and thereby equalizing baroreflex-mediated suppression of MSNA, an important modulator of the final hemodynamic response to exercise, revealed that CKD patients had an exaggerated increase in MSNA during isometric and rhythmic exercise. In addition, mechanoreflex-mediated control was augmented, and metaboreceptor blunting was no longer apparent in CKD patients with baroreflex normalization. Factors leading to mechanoreceptor sensitization, and other mechanisms underlying the exaggerated exercise pressor response, such as impaired functional sympatholysis, should be investigated in future studies.

Published by Elsevier B.V.

1. Exercise intolerance in chronic renal failure

Patients with chronic renal failure (CRF) suffer from exercise intolerance and reduced physical capacity. Both patients with end-stage renal disease (ESRD) on renal replacement therapies and chronic kidney disease (CKD) not yet requiring dialysis have significant impairments in measures of exercise capacity including peak work capacity and peak oxygen uptake (Adams and Vaziri, 2006; Campistol, 2002; Clyne, 1996; Johansen, 1999; Kopple et al., 2005; Moore et al., 1993; Sietsema et al., 2002). The mechanisms underlying exercise intolerance in CRF are multifactorial and not fully understood. Contributing factors include uremic myopathy (Adams and Vaziri, 2006; Bardin, 2003; Campistol, 2002), physical deconditioning (Johansen et al., 2000) as well as abnormal neurocirculatory and hemodynamic responses (Park et al., 2008a, 2012) during exercise.

Abnormal hemodynamic and neurocirculatory control during exercise has been found to be an important pathogenic mechanism underlying the exercise dysfunction of other chronic conditions characterized by exercise intolerance, such as chronic heart failure (CHF) (Clark et al., 1996); however, until recently, its role in the pathogenesis of the exercise intolerance of CRF patients was unknown. The majority of patients with kidney disease have hypertension that is oftentimes difficult to control in part due to chronically elevated SNS activity. Multiple prior studies have demonstrated that baseline sympathetic nerve activity is elevated in both CKD and ESRD, and elevated SNS activity is associated with an increased mortality risk in this population (Converse et al., 1992b; Grassi et al., 2011a; Klein et al., 2003a,b; Park et al., 2008b; Zoccali et al., 2002) The pathogenic mechanisms leading to elevated SNS activity in CRF are multifactorial and include renal afferent nerve activation (Campese and Kogosov, 1995; Katholi et al., 1984; Ye et al., 1997, 2002), decreased neuronal nitric oxide bioavailability (Campese et al., 2002), and increased oxidative stress (Campese et al., 2005, 2004). Given these factors that lead to chronic sympathetic overactivation at rest in CRF, we sought to examine whether abnormal hemodynamic responses, particularly due to abnormalities of sympathetic nerve activation, might contribute to exercise dysfunction in CRF.

A major goal of our laboratory has been to examine the pressor responses during acute exercise in patients with varying degrees of renal failure and the underlying reflex mechanisms that mediate those responses. This review provides a focused discussion of (a) abnormal

* Corresponding author at: Renal Division, Emory University School of Medicine, 1639 Pierce Drive, WMB 338, Atlanta, GA 30322. Tel.: +1 404 321 6111x5178; fax: +1 404 235 3049.
E-mail address: jeanie.park@emory.edu (J. Park).

http://dx.doi.org/10.1016/j.autneu.2014.10.013
1566-0702/Published by Elsevier B.V.

blood pressure (BP) responses in the pathogenesis of exercise dysfunction in CRF; (b) role of abnormal sympathetic nervous system (SNS) control during exercise that partially underlies the augmented hemodynamic response; (c) similarities and key differences in derangements of the exercise pressor reflex between CRF and CHF patients; and (d) future research needs to fill the gaps in our understanding of neurocirculatory control during exercise in CRF.

2. Reflex control of the circulation during exercise

The normal physiologic responses to exercise include an increase in cardiac output and BP that serve to meet the increased metabolic demands of skeletal muscle. The BP response is mediated by a balance between vasoconstrictive and vasodilatory forces induced during exercise. The major vasoconstrictive force is reflex activation of the sympathetic nervous system (SNS) (Kaufman and Hayes, 2002; Seals and Victor, 1991). SNS activity directed to the splanchnic, renal, and nonworking skeletal muscle vasculature limits blood flow to these areas and thereby helps redirect blood flow to the exercising, metabolically active skeletal muscle. However, SNS activity directed to the exercising skeletal muscle itself is counteracted by the generation of local metabolites that inhibit the SNS-mediated vasoconstrictor responses during exercise (Dinenno and Joyner, 2004; Rosenmeier et al., 2003) termed functional sympatholysis. In humans, two major systems control the SNS response during exercise: (1) central command and (2) muscle ergoreflex. Central command refers to a signal arising from within the central nervous system that is linked to the perceived effort of exercise and is important in mediating the increase in heart rate (HR) in anticipation of and during exercise, as well as in eliciting increases in SNS activity only at maximal or near-maximal effort (Victor et al., 1995). The muscle ergoreflexes refer to groups of sensory nerve fibers within the skeletal muscle that send afferent signals to activate central SNS outflow when stimulated during exercise (Kaufman and Hayes, 2002; Seals and Victor, 1991). 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 metaboreflex, with a contribution from central command, is paramount in generating the reflex increases in central sympathetic outflow during static exercise (Mark et al., 1985).

3. Blood pressure responses during exercise in CRF

Our prior studies have shown that patients with ESRD on chronic hemodialysis have an exaggerated increase in systolic blood pressure (SBP) compared to healthy controls during isometric and rhythmic exercise (Park et al., 2008a). During a moderate degree of isometric exercise performed via 3 min of static handgrip exercise (SHG 30%) at 30% of maximum voluntary contraction (MVC), we observed a significantly greater increase in SBP from baseline levels in ESRD patients ($+25.7 \pm 4.0\%$) compared to age-matched controls ($+17.2 \pm 1.7\%$, $p = 0.036$) (Fig. 1A) (Park et al., 2008a). In addition, the pattern of HR responses during the 3 min of SHG 30% was significantly different between the two groups; ESRD patients had a greater increase in HR early during the first minute of exercise, which persisted during the 2nd and 3rd minute of static exercise, consistent with an exaggerated response to central command (Fig. 2).

The reflex mechanisms underlying the BP response to exercise can be sorted out using a sequence of maneuvers. The contribution of the muscle metaboreflex to this exaggerated pressor response can be isolated from central command and the mechanoreflex by a maneuver called post-handgrip circulatory arrest (PHG-CA). A blood pressure cuff is inflated on the exercising arm to supra-systolic levels at the conclusion of exercise, trapping the ischemic metabolites in the exercising muscle bed, and then exercise is stopped, thereby disengaging central command and the muscle mechanoreflex. During this PHG-CA maneuver, ESRD patients had exaggerated SBP responses compared to controls, consistent with an exaggerated metaboreflex (Fig. 1B). Low-level rhythmic handgrip exercise (RHG) at 20% MVC was then performed to isolate the mechanoreflex from metaboreflex since this low-level rhythmic exercise produces insufficient ischemic metabolites to engage metaboreceptors (Batman et al., 1994). Low-level RHG (20%) elicited an exaggerated BP response in ESRD patients compared to controls (Fig. 1C), consistent with exaggerated muscle mechanoflex in ESRD patients compared to controls. However, low-level RHG may also engage central command, so passive movement of the volunteers' hand was performed to eliminate central command from mechanoreflex stimulation. Passive hand movement is performed by the investigator moving the subject's hand rhythmically, inducing muscle stretch at the wrist and thereby stimulating muscle mechanoreceptors. The subject remains passive and does not initiate the movement, thereby eliminating central command. Once again, an exaggerated BP response was elicited in ESRD patients compared with controls (Fig. 1D), further supporting the concept that the muscle mechanoreflex control of BP was augmented in ESRD. To rule out a generalized, non-specific hypertensive response to all sympathoexcitatory stimuli, the cold pressor test (CPT) was performed and BP was measured. In contrast to exercise, during CPT, there was no significant difference in SBP response during this non-exercise pressor stimulus between the ESRD group and controls (data not shown), suggesting that the exaggerated pressor response during SHG 30% and RHG 20% was specific to exercise, and was not generalized to all sympathoexcitatory stimuli.

We then asked the question whether this exaggerated hypertensive response to exercise was present earlier in the progression of renal failure; that is, did patients with less severe renal disease also exhibit an exaggerated reflex hypertensive response to exercise? In a subsequent study in patients with stage II or early stage III CKD (Park et al., 2012), with a mean serum Cr of 1.7 mg/dL and eGFR of 54 mL/min, BP responses were compared in response to moderate SHG and low-level RHG exercise (Fig. 3) and were exaggerated, consistent with augmented muscle mechanoreflex control of BP in these patients with mild to moderate CKD compared to hypertensive controls without renal impairment. There were no differences in HR responses during exercise in CKD patients, suggesting lack of augmented BP response due to central command. A strength of this follow-up study was the comparison of hypertensive CKD patients with well-matched hypertensive controls, isolating reduced renal function, rather than comorbid conditions or the dialysis procedure, as the variable associated with the abnormal exercise pressor response. In additional studies, these exaggerated BP responses were present in response to PHG-CA, consistent with augmented muscle metaboreflex control of BP during exercise in early CKD.

In summary, these results demonstrate a clinically important finding that patients with reduced renal function have an exaggerated pressor response during isometric and rhythmic exercise, and that these hemodynamic abnormalities begin early in the course of renal disease. Augmented increases in pressor responses during exercise could contribute to the pathogenesis of exercise intolerance in CKD by increasing myocardial workload, increasing peripheral resistance, altering muscle blood flow, and contributing to the development of uremic myopathy. Furthermore, exaggerated pressor responses during exercise have been shown to correlate with an increased risk of cardiovascular disease in healthy humans (Jae et al., 2006; Sharabi et al., 2001). Thus, exaggerated pressor responses may contribute to the increased risk of cardiovascular disease and sudden death that characterizes patients with reduced renal function (Matsushita et al., 2010).

4. Sympathetic nervous system regulation during exercise in CRF

The mechanisms underlying the exaggerated pressor response to exercise in patients with renal failure are unclear. Multiple prior studies