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Abnormal Neurocirculatory Control During Exercise in Humans with Chronic Renal Failure

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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.

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

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oxygen uptake (Adams et al., 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 et al., 2006; Bardin, 2003; Campistol, 2002), physical deconditioning (Johansen et al., 2000), as well as abnormal neurocirculatory and hemodynamic responses (Park et al., 2008a; Park et al., 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; Klein et al., 2003b; Park et al., 2008c; Zoccali et al., 2002) The pathogenic mechanisms leading to elevated SNS activity in CRF are multifactorial, and include renal afferent nerve activation (Campese et al., 1995; Katholi et al., 1984; Ye et al., 1997; Ye et al., 2002), decreased neuronal nitric oxide bioavailability (Campese et al., 2002), and increased oxidative stress (Campese et al., 2005; Campese et al., 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 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.

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 et al., 2002; Seals et al., 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 et al., 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 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 et al., 2002; Seals et al., 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).

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 minutes 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 ± 4.0%) compared to age-matched controls (+17.2 ± 1.7%, p=0.036) (Figure 1A) (Park et al., 2008b). In addition, the pattern of HR responses during the 3 minutes 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 (Figure 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 (Figure 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 (Figure 1C), consistent with exaggerated muscle mechanoflex in ESRD patients compared to controls. But 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 (Figure 1D), further supporting the concept that 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 RHG20% 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 (Figure 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 contribute 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).

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 have demonstrated that SNS activity is chronically elevated in patients with both mild to moderate CKD (Grassi et al., 2011a; Klein et al., 2003a; Klein et al., 2003b; Ligtenberg et al., 1999), as well as ESRD (Converse et al.,

1992b; Park et al., 2008c); thus, we proposed in the next series of studies that dysregulation of SNS activity, specifically overactivation of central SNS output during exercise, may be one culprit underlying the exaggerated pressor response.

We hypothesized that sympathetic nerve activity directed to muscle (MSNA), directly recorded using the technique of microneurography, would be elevated during exercise in patients with ESRD and in those with mild to moderate CKD compared to controls with normal renal function. Surprisingly, in the initial experiments conducted in ESRD patients (Park et al., 2008a), we observed that muscle sympathetic nerve activity (MSNA) responses during SHG 30% were not significantly elevated in ESRD patients compared to controls ($p=0.28$). Further, during low-level RHG and passive exercise, MSNA responses were not augmented in ESRD patients compared to controls, apparently refuting our hypothesis that muscle mechanoreflex control of MSNA is augmented in ESRD patients. Most surprising, during PHG-CA, MSNA actually fell to baseline levels, unlike controls in whom MSNA remained elevated, consistent with an attenuated control of MSNA during metaboreflex isolation in ESRD. Our initial conclusions from these baseline studies were that in ESRD patients: a) there were no observed exaggerated increases in SNS response during static exercise; b) muscle metaboreflex activation of MSNA may be blunted in ESRD, as has been described in other chronic disease conditions such as heart failure (Sterns et al., 1991), obesity (Negrao et al., 2001; Trombetta et al., 2003), essential hypertension (Rondon et al., 2006), and aging (Markel et al., 2003); and c) in contrast to heart failure in which mechanoreflex control of SNS activation during exercise is heightened (Middlekauff et al., 2004; Middlekauff et al., 2001), there were no differences in MSNA responses during mechanoreflex isolation compared to controls.

We acknowledge from the results above that exaggerated sympathetic activation cannot be the sole mechanism underlying the augmented pressor response during exercise in ESRD, since MSNA responses during static, rhythmic, and passive exercise were all similar to controls. Indeed, these findings point to the importance of non-neural mechanisms influencing the final hemodynamic response, such as impaired functional sympatholysis. Functional sympatholysis refers to the phenomenon that during exercise, despite an increase in central sympathetic output, vasoconstriction does not occur in exercising skeletal muscle because of local factors such as nitric oxide (NO) and adenosine that maintain blood flow to the working skeletal muscle (Dinenno et al., 2004; Rosenmeier et al., 2003). Functional sympatholysis has never previously been tested in CKD patients, but impaired functional sympatholysis could lead to reduced conductance to metabolically active muscle during exercise, and contribute to exercise intolerance and exaggerated pressor responses. Alternatively, greater vascular alpha 1-adrenergic responsiveness is another potential mechanism contributing to the greater blood pressure response for a similar degree of increase in SNS activity observed in CKD patients. In vitro studies conducted on vascular smooth muscle cells derived from a polycystic kidney disease model revealed enhanced vasoconstriction in response to phenylephrine stimulation (Qian et al., 2007), and augmented renal vasoconstrictor responses in animal models of hypertensive renal failure were mediated by greater alpha 1 receptor responsiveness (Hye Khan et al., 2008). One prior human study suggested that that ESRD patients receiving erythropoietin had increased vascular alpha 1-adrenergic sensitivity (Abiose et al., 2007). Whether impaired functional

sympatholysis and/or increased vascular alpha 1 receptor responsiveness contributes to the exaggerated BP response during exercise in CRF has yet to be investigated..

Although non-neural mechanisms likely contribute importantly to the augmented pressor response during exercise in CKD, we did not exclude a contributory role of increased sympathetic activation on the augmented exercise pressor response which we investigated in more detail in the next series of studies.. Our rationale for this position stemmed from two major observations. First, in healthy humans, arterial baroreflex buffering of MSNA remains intact during exercise (Scherrer et al., 1990); that is, arterial baroreflexes continue to modulate central sympathetic output, but at a higher setpoint, regulating the final BP response. Secondly, although debatable and not directly tested in our study population, prior reports using pharmacologic manipulation of arterial BP with phenylephrine and nitroprusside infusions have shown that sympathetic arterial baroreflex sensitivity is intact in ESRD patients (Converse et al., 1992a; Klein et al., 2003a; Ligtenberg et al., 1999). Therefore, our observation that MSNA responses during exercise were not blunted, and were in fact equivalent to that of controls, in CKD in the setting of an augmented pressor response, suggested that augmented sympathetic outflow may have been masked by baroreflex-mediated suppression, and may thus still play a contributory role in the exaggerated pressor response.

In the next series of experiments (Park et al., 2012), we investigated this hypothesis by examining the exercise pressor reflex in patients with mild to moderate CKD in the setting of pharmacological manipulation of BP, in order to equalize BP responses during exercise between CKD patients and controls, and thereby equalize arterial baroreflex restraint of SNS activity during exercise between the groups. We successfully titrated weight-based doses of intravenous nitroprusside (NTP) to equalize the BP response to SHG 30%, metaboreflex isolation via PHG-CA, and mechanoreceptor isolation via RHG 20% in CKD patients compared to matched hypertensive controls (Figure 3). SNS responses were measured during NTP infusions in CKD patients, and during 5% dextrose (D5W) infusions in CKD patients and in controls for comparison. Equalizing BP and baroreflex restraint pharmacologically during these maneuvers revealed that CKD patients had exaggerated increases in MSNA during SHG 30%, supporting the notion that sympathetic outflow in response to exercise is in fact exaggerated when baroreflex restraint was equalized (Figure 3A and 3B). In addition, when the exaggerated BP response was ameliorated with NTP during PHG-CA, MSNA was no longer blunted, consistent with intact (but not exaggerated) metaboreflex-mediated control of MSNA (Figure 3C and 3D). Most importantly, during RHG 20%, MSNA responses were significantly augmented, consistent with exaggerated muscle mechanoreflex control of MSNA in CKD (Figure 3E and 3F). An acknowledged limitation of these studies is that NTP was only administered to CKD patients and not administered to controls, in order to eliminate a possibility of an increased MSNA response due to NTP that was independent of a change in blood pressure. However, a direct sympathoexcitatory effect of NTP is unlikely.

In summary, these studies in which baroreflex restraint on MSNA was equalized during exercise in CKD reveals that 1) SNS activation is exaggerated during acute isometric exercise; 2) muscle metaboreflex-mediated increases in MSNA are not blunted; and 3)

muscle mechanoreflex-mediated increases in MSNA are heightened in CKD compared to controls. Finally, SNS activity remains inappropriately high in CKD in the setting of augmented BP responses during exercise, and may therefore be a contributory factor in the exaggerated exercise pressor response in these patients

Comparing and contrasting the exercise pressor reflex in heart failure versus renal failure: what can we learn about exercise intolerance in 2 distinct chronic conditions?

The exercise pressor reflex has been more thoroughly investigated in patients with CHF. Considering our findings in CRF in the context of what is known about muscle ergoreflex control in CHF allows us to note key similarities and distinctions that may help define the role of abnormal neurocirculatory control of exercise dysfunction in two chronic conditions (Figure 4), as well as help delineate key areas of future study in CRF. In prior studies, we, and others, have shown that muscle ergoreflex control of SNS activity during exercise is abnormal in patients with CHF, a disease with similar features as CRF of baseline SNS overactivity and profound exercise intolerance (Clark et al., 1996; Khan et al., 2000; Middlekauff et al., 2004; Middlekauff et al., 2001; Sinoway et al., 2005). CRF and CHF share similar features of heightened resting sympathetic tone, a skeletal myopathy, and exercise dysfunction that is independent of the severity of the primary disease process (i.e. occurs in both mild and severe heart failure, as well as mild and severe renal failure (Johansen et al., 2012)).

In CHF, the overall MSNA response to isometric and rhythmic exercise is not different from that of controls. Similarly, in baseline studies without manipulation of arterial BP, MSNA responses during exercise in ESRD and CKD are similar to that of controls; however, one key difference is that in CRF patients, these responses occur in the setting of an exaggerated BP response during exercise. This finding suggests a key role of non-neural mechanisms that contribute to the heightened exercise pressor response in CRF. One potential mechanism yet to be investigated is impairment in NO-mediated vasodilatation during exercise that may be influenced by the uremic milieu. Concomitant with reflex SNS activation, in healthy humans exercise induces an intense vasodilatory response that increases blood flow in working skeletal muscles to match the increased oxygen demand (Gilligan et al., 1994; Goto et al., 2003; Katz et al., 1996; Maiorana et al., 2003; Saltin, 2007). Vasodilation is achieved by both inhibiting the SNS mediated vasoconstrictor response locally (by blocking the action of NE released at sympathetic nerve endings (Dinenno et al., 2004; Rosenmeier et al., 2003)) termed functional sympatholysis, as well as by the vasodilatory effects of locally generated or released vasoactive substances (Saltin, 2007). NO plays an important role in exercise-induced vasodilatation (Dyke et al., 1995; Gilligan et al., 1994; Goto et al., 2007; Hickner et al., 1997) via direct effects, as well as contributing to functional sympatholysis by blocking post-junctional alpha-1 receptors (Dinenno et al., 2004; Rosenmeier et al., 2003). Patients with CRF have high levels of the uremic toxin asymetric dimethyl arginine (ADMA) (Grassi et al., 2011b; Mallamaci et al., 2004; Ravani et al., 2005; Vallance et al., 1992; Zoccali, 2006; Zoccali et al., 2001), an endogenous inhibitor of NO synthase that accumulates in patients with renal failure, and

leads to decreased NO bioavailability. Whether impaired NO-mediated vasodilatation, and/or impaired functional sympatholysis, contributes to the exaggerated exercise pressor response in CRF is unknown, but likely.

Studies of the exercise pressor reflex in CHF have shown that muscle mechanoreflex activation of SNS activity is augmented (Middlekauff et al., 2004; Middlekauff et al., 2001), muscle metaboreceptor control is markedly blunted (Sterns et al., 1991), and the overall SNS response to acute exercise is similar to that of healthy controls. In contrast to CHF, CKD patients, when BP responses and arterial baroreflex restraint during exercise are equalized, have an exaggerated overall MSNA response during exercise, without blunting of metaboreflex control; however, similar to CHF under basal conditions, muscle mechanoreflex control is augmented in CKD. Although muscle mechanoreceptors primarily function as stretch receptors, these thinly myelinated group III afferent nerve fibers are pleiotropic and can become sensitized by metabolic products that are generated during exercise and accumulate in the muscle interstitium to activate muscle afferent nerves (Kaufman, 2012). Previous studies done by our group in CHF have demonstrated a role for cyclooxygenase products, but not adenosine or lactate, in sensitizing muscle mechanoreceptors (Middlekauff et al., 2004; Middlekauff et al., 2008). Other studies in peripheral artery disease models have shown that adenosine triphosphate (ATP) sensitizes mechanoreceptors via upregulation of purinergic 2X (P2X) receptors at nerve endings (Stone et al., 2014). Whether these or other ischemic or uremic metabolites sensitize muscle mechanoreceptors in CRF remain untested.

The role of central command in the exaggerated exercise pressor response in these two chronic conditions is less clear. HR responses were augmented early on during acute exercise in ESRD patients, but not in CKD patients or CHF patients, suggesting that SNS activation mediated by central command may be augmented in patients with severe renal failure, but not in patients with milder renal dysfunction, or heart failure. The potential role of central command on abnormal sympathetic and pressor responses during exercise in these conditions should be further investigated.

One limitation of microneurographic studies is that we are limited to making measurements of sympathetic nerve activity directed to muscle (MSNA). Although MSNA has been shown to correlate with whole body, cardiac, and renal norepinephrine spillover (Wallin et al., 1992; Wallin et al., 1996), SNS activity directed to other organs were not measured in prior studies. Therefore, sympathetic activation directed to other vascular beds, such as cardiac and renal, and how this might influence abnormal neurocirculatory and blood pressure responses during exercise in CRF patients, remains unknown. In chronic heart failure, prior studies have shown that patients with CHF have exaggerated renal vasoconstriction during acute exercise (Middlekauff et al., 2000; Middlekauff et al., 2001). Exaggerated renal vasoconstriction during exercise could lead to increased elaboration of renin, volume retention, and increased blood pressure. Whether CRF patients have abnormal cardiac or renal sympathetic tone during exercise should be investigated in future studies.

Summary and Future Directions

Patients with both mild renal dysfunction, as well as severe renal failure, exhibit abnormalities of neurocirculatory control during exercise characterized by an exaggerated pressor response, and augmented SNS response mediated by heightened mechanoreflex mediated activation. These reflex hemodynamic and neurocirculatory abnormalities contribute to exercise intolerance, uremic myopathy, and increased risk of cardiovascular events and sudden death in patients with CRF. Although some progress has been made in recognizing the importance of these derangements in the exercise intolerance of renal failure, key gaps in our understanding of the exercise pressor response in CRF exist. One important area of future investigation is to determine the role of impaired NO-mediated vasodilatation with subsequent endothelial dysfunction and impaired functional sympatholysis on the final hemodynamic response during acute exercise in CRF. Secondly, examination and identification of ischemic or uremic metabolites that sensitize muscle mechanoreceptors in CRF should be investigated. Third, the potential role of abnormal regulation by central command should be further explored. Finally, whether interventions such as exercise conditioning may ameliorate the augmented pressor and sympathetic responses in CRF, and modulate mechanoreceptor sensitization, is clinically relevant and of paramount importance.

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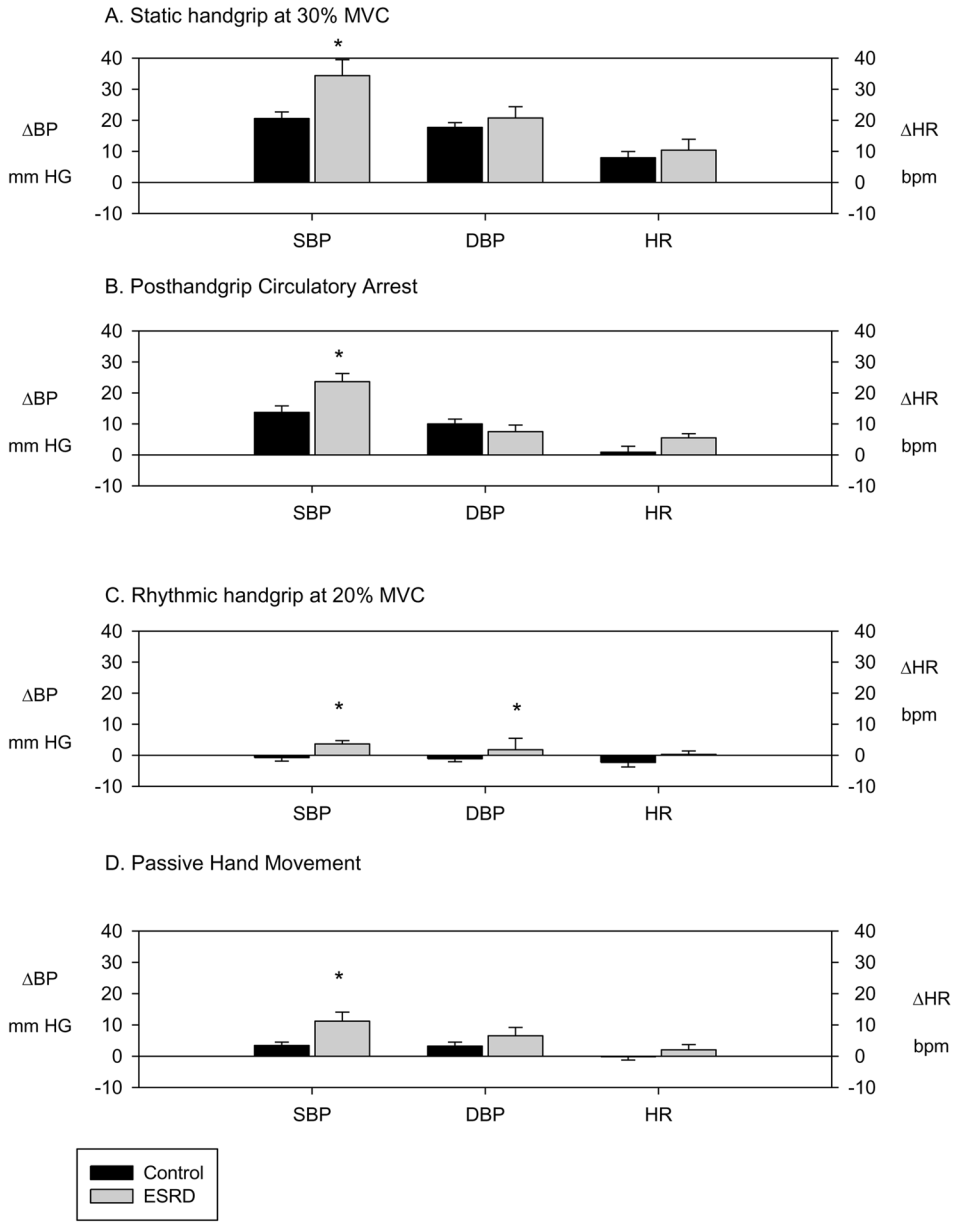

Figure 1. Hemodynamic changes during experimental maneuvers (Park et al., 2008a)

Change in systolic (SBP) and diastolic blood pressure (DBP) in mm HG, and change in heart rate (HR) in beats per minute (bpm) depicted during each experimental maneuver in control participants (black bars) and end-stage renal disease (ESRD) patients (gray bars). MVC indicates maximum voluntary contraction. Values are expressed as means ± SE. *Significant p-value < 0.05 compared to Controls.

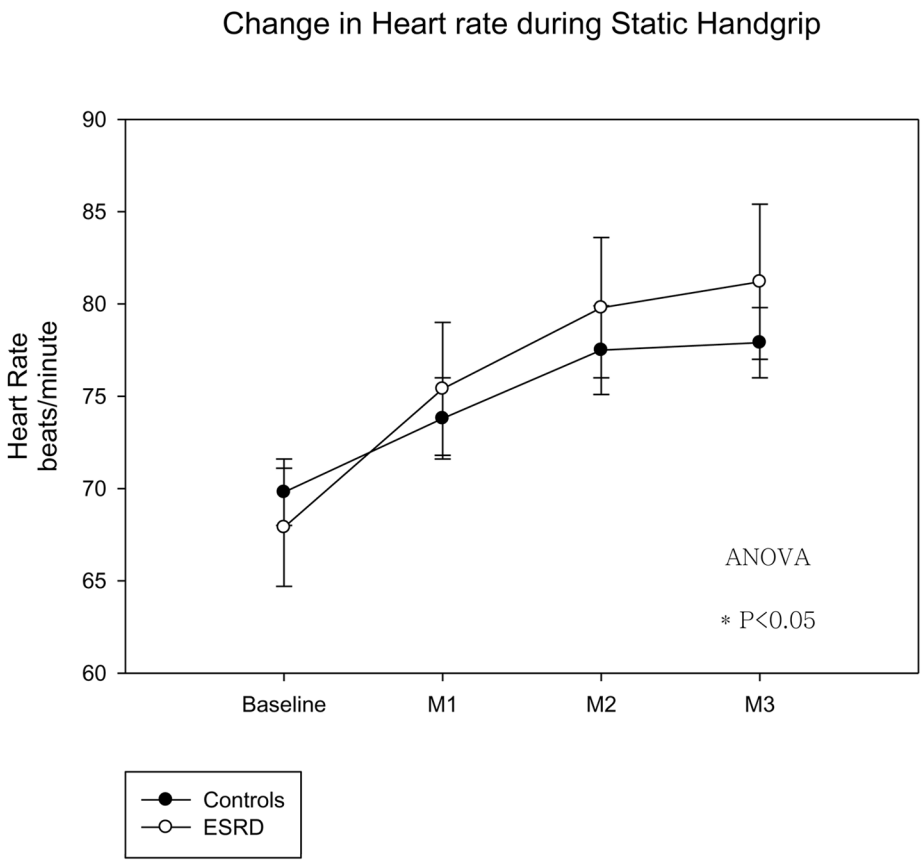

Figure 2.

Change in heart rate during 3 minutes of moderate static handgrip exercise. *Overall ANOVA F-test is significant for a difference in change in heart rate with exercise between ESRD patients and Controls.

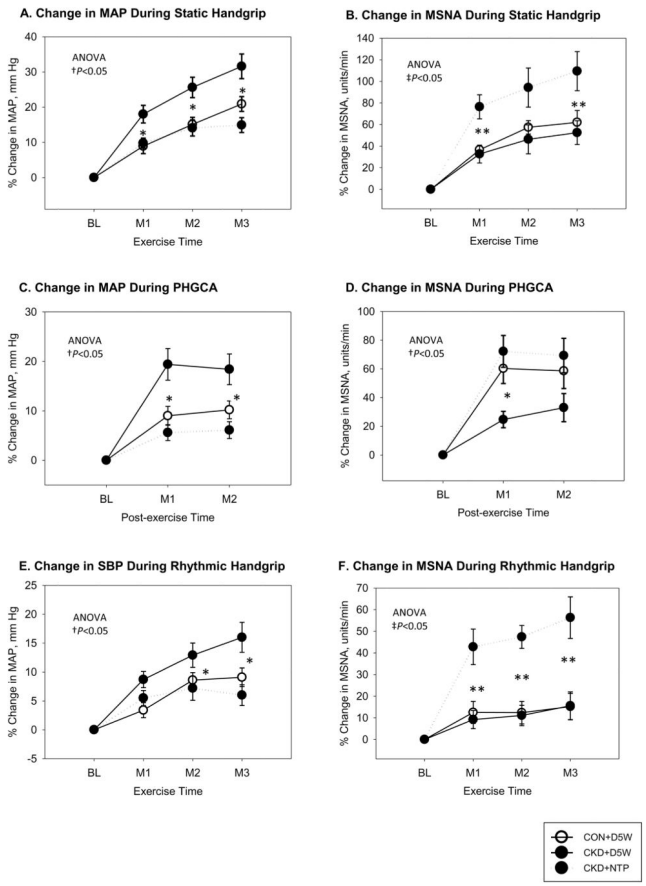

Figure 3. Change in MAP and MSNA during exercise (Park et al., 2012)

Change in mean arterial pressure (MAP) and muscle sympathetic nerve activity (MSNA) total activity in controls infused with 5% Dextrose (CON+D5W), chronic kidney disease (CKD) patients infused with D5W (CKD+D5W), and CKD patients infused with nitroprusside (CKD+NTP) during: (A and B) static handgrip; (C and D) post-handgrip circulatory arrest (PHGCA); (E and F) rhythmic handgrip. Values are expressed as means ± SE. †Indicates overall ANOVA F-test was significant for a difference between CON+D5W versus CKD+D5W groups (see results section). *Indicates p-value < 0.05 for a difference between CON+D5W versus CKD+D5W groups at that time point.

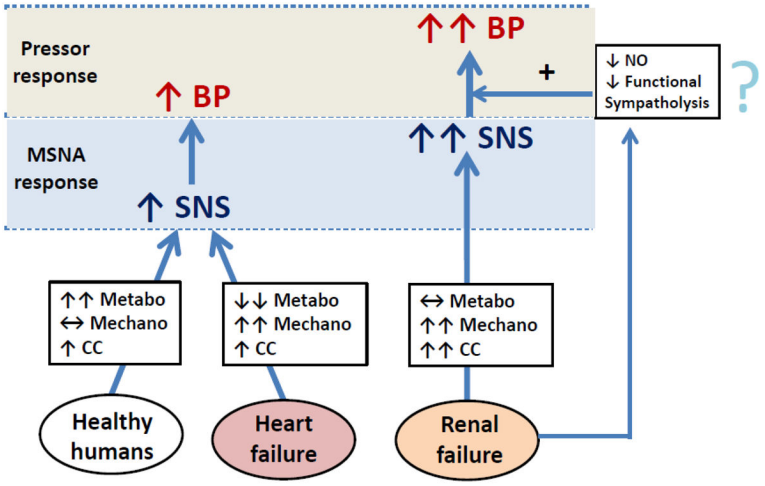

Figure 4.

The Exercise Pressor Reflex in Healthy Humans, Heart Failure Patients, and Renal Failure Patients. In healthy humans, metaboreflex (Metabo) control is paramount in generating the reflex activation of sympathetic nervous system (SNS) activation, with resultant increase in blood pressure (BP) during exercise. Central command (CC) contributes to the increase in BP, mostly through an increase in heart rate, whereas the Mechanoreflex (mechano) contributes minimally to the exercise pressor reflex in healthy humans. In contrast, heart failure patients have blunted metaboreflex, and augmented mechanoreflex mediated increases in SNS during exercise. Similarly, in renal failure patients, mechanoreflexes are also augmented; and the metaboreflex contribution to sympathetic activation is intact, leading to an overall exaggerated increase in SNS activation that contributes to an exaggerated BP response during exercise. The role of central command during exercise in chronic renal failure (and heart failure) needs further study. In renal failure, mechanisms outside the exercise pressor reflex, such as decreased nitric oxide (NO) bioavailability, and decreased functional sympatholysis also likely contribute to the exaggerated exercise BP response.