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Review

Central mechanisms for exercise training-induced reduction in sympatho-excitation in chronic heart failure

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ABSTRACT

The control of sympathetic outflow in the chronic heart failure (CHF) state is markedly abnormal. Patients with heart failure present with increased plasma norepinephrine and increased sympathetic nerve activity. The mechanism for this sympatho-excitation is multiple and varied. Both depression in negative feedback sensory control mechanisms and augmentation of excitatory reflexes contribute to this sympatho-excitation. These include the arterial baroreflex, cardiac reflexes, arterial chemoreflexes and cardiac sympathetic afferent reflexes. In addition, abnormalities in central signaling in autonomic pathways have been implicated in the sympatho-excitatory process in CHF. These mechanisms include increases in central Angiotensin II and the Type 1 receptor, increased in reactive oxygen stress, upregulation in glutamate signaling and NR1 (N-methyl-D-aspartate subtype 1) receptors and others. Exercise training in the CHF state has been shown to reduce sympathetic outflow and result in increased survival and reduced cardiac events. Exercise training has been shown to reduce central Angiotensin II signaling including the Type 1 receptor and reduce oxidative stress by lowering the expression of many of the subunits of NADPH oxidase. In addition, there are profound effects on the central generation of nitric oxide and nitric oxide synthase in sympatho-regulatory areas of the brain. Recent studies have pointed to the balance between Angiotensin Converting Enzyme (ACE) and ACE2, translating into Angiotensin II and Angiotensin 1–7 as important regulators of sympathetic outflow. These enzymes appear to be normalized following exercise training in CHF. Understanding the precise molecular mechanisms by which exercise training is sympatho-inhibitory will uncover new targets for therapy.

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1. Introduction

The syndrome of chronic heart failure (CHF) impacts every organ system including skeletal muscle both at rest and during exercise (Drexler et al., 1987; Hambrecht et al., 2000; Just, 1991; Magnusson, 1995; Musch et al., 1989; Parmley, 1989; Riley et al., 1990). Further, exercise was initially thought to worsen left ventricular dysfunction in CHF patients (McDonald et al., 1972). One of the most frequent complaints of patients with even mild CHF is the inability to exercise. One would think that the mechanism at the root cause of exercise intolerance in CHF is simply a lack of cardiac reserve and an inability to adjust cardiac output to workload. However, because CHF impacts sympathetic outflow, endothelial function, peripheral vascular resistance and skeletal muscle protein synthesis and metabolism, the mechanism of exercise intolerance is multifactorial in this disease state. While the standard of care for CHF

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in the mid-20th century was bed rest and diuretic and/or cardiac glycoside therapy it has become increasingly accepted that all but the most severe CHF patients can carry out some form of exercise (Downing and Balady, 2011; McKelvie, 2008). In fact, the American Heart Association has advocated exercise training as a safe form of therapy (Pina et al., 2003). Several clinical studies now show substantial benefits of exercise training in patients with CHF including quality of life, a reduction in hospitalization, cardiac events and survival (Belardinelli et al., 1999; Chicco et al., 2008; Piepoli and Capucci, 2000). The HF-ACTION trial demonstrated a decrease in all-cause mortality and hospitalization in CHF patients who underwent a moderate exercise training regimen (aerobic exercise of either cycling or treadmill walking for 40 min at 60% to 70% of heart rate reserve, five times per week) (O'Connor et al., 2009). These benefits are not limited to a single type of exercise modality; resistance training, aerobic exercise, and even calisthenics as tolerated after a cardiac event are all considered to be effective (Piepoli and Capucci, 2000). In fact, a reduction of physical activity in this same CHF patient population may be a contributor to future exercise intolerance and impaired peripheral vascular resistance (Hunt et al., 2005). While there is consensus that exercise training is beneficial in the CHF state, the underlying mechanisms responsible for these effects are not at all clear. Pre-clinical experimental studies have been extremely useful in shedding light on potential pathophysiological mechanisms. This review will focus primarily on the effects of exercise training on sympathetic and cardiovascular reflex function in CHF however, it should be kept in mind that change in sympathetic outflow is just one mechanism responsible for the beneficial effects of exercise training in CHF.

2. Sympatho-excitation in CHF

The neural control of cardiovascular function relies on an ancient controller dominated by classical negative feedback servo control systems scattered throughout the cardiovascular system. Normally, just the right amount of sympathetic nerve activity is provided to maintain peripheral vascular resistance and arterial pressure at a set point necessary for adequate tissue perfusion. The sensors are primarily located in the great vessels (baroreceptors), the heart, and in the carotid and aortic bodies (chemoreceptors). A large number of studies, both basic and clinical, have shown marked abnormalities in the ability of these sensors to correctly transmit information concerning arterial pressure, blood volume and oxygen tension (Eckberg et al., 1971; Ellenbogen et al., 1989; La Rovere et al., 2009; Mohanty et al., 1989; Ponikowski et al., 1997; Zucker, 1991) in the setting of CHF. Early work suggested that depression in baroreflex gain mediated sympatho-excitation in patients and animals with CHF (Ferguson et al., 1984, 1992; Mancia et al., 1992). Reflexes mediated by sensory endings in the low pressure side of the circulation have also been shown to exhibit reduced gain and contribute to sympatho-excitation by removal of inhibitory restraint (Patel et al., 1996a; Pliquett et al., 2003; Zheng et al., 2006). Further studies also suggested that an increase in chemoreceptor sensitivity in CHF drives sympatho-excitation (Chua and Coats, 1997; Chua et al., 1996; Chugh et al., 1996; Ponikowski et al., 1997; Schultz and Li, 2007; Sun et al., 1999a,b). Finally, excitatory input from the so-called "cardiac sympathetic afferents" has also been shown to be augmented in the CHF state (Gao et al., 2004b, 2005a, 2007a; Wang and Zucker, 1996; Wang et al., 2006; Zhu et al., 2002, 2004a,b). While there is little doubt that these reflexes contribute to sympatho-excitation in CHF the question still remains as to whether these abnormalities are initiating factors or a consequence of the CHF state?

In addition to dysfunction in cardiovascular sensory function there are many alterations in various components in the reflex arcs mediating autonomic outflow in CHF. Central changes in synaptic transmission and membrane sensitivity of pre-sympathetic neurons at several hypothalamic and medullary sites also participate in sympatho-excitation in CHF. Changes in discharge sensitivity of neurons in the rostral ventrolateral medulla (RVLM) and in the paraventricular nucleus (PVN) have been prominent in this regard (Gao et al., 2008; Patel et al., 2000). While it is beyond the scope of this review to detail all of the central changes that take place in CHF some of these changes will be highlighted below because exercise training profoundly influences them.

3. Does exercise training lower sympathetic outflow in heart failure?

Studies carried out on patients with CHF have shown a reduction in sympathetic outflow following a supervised exercise training regimen (stationary cycling 60 min 3 times per week), measured by either direct recording of muscle sympathetic nerve activity (Fraga et al., 2007; Roveda et al., 2003) or urinary norepinephrine excretion (Yousufuddin et al., 2000). Softer indices of sympatho-excitation such as heart rate variability and power spectral analysis have also pointed to a lowering of sympathetic outflow following exercise training in the CHF population (Coats et al., 1992; Colombo et al., 1999; Scalvini et al., 1998). These indices coincide with improvement in baroreflex and chemoreflex sensitivity in CHF (Gao et al., 2007b; Li et al., 2008; Liu et al., 2000, 2002; Negraõ and Middlekauff, 2008a,b). In a recent study by Rengo et al. (2014) it was shown that exercise training resulted in a decrease in heart rate, plasma norepinephrine, and brain natriuretic peptide (BNP) while increasing maximal oxygen consumption (MVO_2) and ejection fraction slightly. Importantly, these data were prognostic as to outcomes. Those patients with the greatest change in norepinephrine and BNP exhibited significantly better survival profiles. These data support earlier work showing that mortality was reduced in CHF patients that underwent an exercise training program (Belardinelli et al., 1999; Hagerman et al., 2005; Keteyian et al., 2012; O'Connor et al., 2009; Rosenwinkel et al., 2001; Smart and Marwick, 2004). On the other hand, a recent analysis of the HF ACTION database by Ahmad et al. (2014) showed no effect on BNP or cardiac function but an improvement in hospitalizations and survival. In total however, it seems clear that exercise training does indeed impact sympathetic outflow and survival if not cardiac function per se.

4. What central mechanisms are responsible for sympatho-inhibition following exercise training in CHF?

The discharge sensitivity of pre-sympathetic neurons in the RVLM and of sympathetic projecting neurons in the PVN is determined ultimately by activity in membrane ion channel proteins and currents. In the CHF state alterations in several neuronal signaling pathways have been defined that impact channel activity and may be impacted by exercise training. The focus of this work has largely been in three areas; 1. The renin-Angiotensin II (Ang II) system, 2. reactive oxygen stress (ROS) and 3. nitric oxide synthase (NOS). In addition, exercise training impacts glutamate signaling in CHF (Kleiber et al., 2008; Llewellyn et al., 2012). Sympatho-excitatory neurons in the RVLM and PVN express Angiotensin II Type 1 receptor (AT1R) (Gao et al., 2005b, 2008; Liu et al., 2000; Wang et al., 2004) that modulate sympathetic discharge when stimulated with Ang II (Gao et al., 2008). Experiments in various species and models of CHF have shown that AT1R protein and mRNA are increased in CHF in these sympatho-excitatory regions (Gao et al., 2005b). Signaling through the AT1R increases neuronal excitability, in part, by increasing superoxide production through activation of NADPH oxidase. Following an exercise training regimen rabbits with CHF exhibit a profound reduction in renal sympathetic nerve activity at rest, and normalization of plasma Ang II (Fig. 1) (Liu et al., 2000). In addition, exercise trained CHF rabbits exhibited a decrease in AT1R expression in the RVLM (Gao et al., 2004a, 2005b), a decrease in central oxidative stress (Gao et al., 2007b) and an increase in both CuZn and Mn superoxide dismutase (SOD) (Gao et al., 2004a). Importantly, the changes in central AT1R expression, baseline sympathetic nerve activity and the improvement in baroreflex function could be prevented by concomitant systemic infusion of Ang II in order to prevent the normalization of Ang II by exercise training (Fig. 1) (Mousa et al., 2008). These data fit with the idea that Ang II, derived either from de novo synthesis