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COMMENT

Exercise in treatment-resistant hypertension. A natural neuromodulation therapy?

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Current guidelines recommend adopting lifestyle changes as the first line of therapy to manage hypertension [1]. In particular, a large body of evidence supports the non-pharmacological antihypertensive effects of dynamic aerobic exercise [1]. In this issue of the journal, a paper by Lopez et al. reports the results of EnRicH (Exercise Training in the Treatment of Resistant Hypertension) as a prospective, single-blind, randomized clinical trial. Sixty patients were randomized to 12 weeks of aerobic exercise training (ExT) or usual care. The ExT program reduced central BP and improved cardiovascular disease risk biomarkers of angiotensinII (AngII) and superoxide dismutase in treatment-resistant hypertensives (TRH) [2]. Increased central BP in TRH is associated with exacerbation of heart failure (HF), and it has been pointed out that left ventricular (LV) afterload reduction, AngII reduction, and antioxidant effects due to ExT might all act to suppress worsening HF.

TRH is associated with increased risk of adverse cardiovascular events, especially HF [3]. Although the pathophysiological mechanisms underlying TRH development are not fully understood, increased sympathetic nervous system (SNS) activity, increased renin-angiotensin-aldosterone system (RAAS), and sodium uptake/retention are predominantly associated with TRH [4]. Although oxidative stress may not be the only cause of hypertension, it amplifies BP elevation in the presence of increased SNS, RAAS activation and salt loading in experimental models [5]. TRH is also associated with an increase in the inflammatory markers of tumor necrosis factor (TNF)-α and interleukin-6 and a reduction in levels of transforming growth factor beta-1 [6]. Congestive HF is typically characterized by increased SNS drive, low-grade inflammation and altered fluid regulation. Regular ExT improves functional capacity and quality of life, and significantly attenuates increased SNS drive in HF [7].

Many studies support the idea that the cardiovascular system is regulated by the central autonomic network, which includes the insular cortex (Ic), anterior cingulate gyrus, and amygdala [4]. A recent study on Ic stimulation showed that interhemispheric differences exist in vasoregulatory function, with the right Ic involved in vasoconstriction and the left Ic in vasodilation [8]. While tachycardia/pressor effect was common after right anterior Ic stimulation, bradycardia/depressor effect was common after left posterior Ic stimulation [9]. Thus, right Ic is predominantly associated with sympathetic tone, while left posterior Ic is predominantly associated with vagal tone. In addition, dense reciprocal connections are observed between the insular cortex and subcortical autonomic centers of the nucleus tractus solitarius (NTS) [10, 11], the parabrachial nucleus [12], the hypothalamic paraventricular nucleus (PVN) [13] and the lateral hypothalamic area [14], and these autonomic core centers also have reciprocal connections with each other [4].

The autonomic adjustments to exercise are mediated by central signals from the higher brain, so-called 'central command', and by a peripheral reflex arising from working skeletal muscle [15]. Neural elements distributed throughout the cardiac nervous system, from the level of the Ic to the intrinsic cardiac nervous system, constantly interact with

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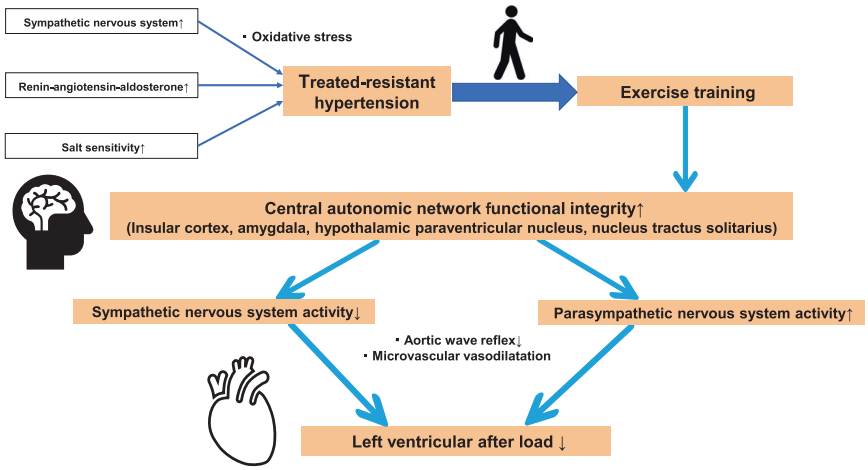

Fig. 1 A possible scheme for the relationship between exercise and left ventricular afterload reduction in treatment-resistant hypertension

each other to ensure that cardiac output matches the dynamic processes of regional blood flow demand [16]. In a human study, a conjunction analysis showing common responses to handgrip and attempted foot lifting revealed activation of the right central Ic consistent with the concept of the 'central commands' feedforward hypothesis [17]. The left Ic activity was significantly increased during active cycling, but not during passive cycling [18]. In addition, decreased activity of the Ic and thalamus is an important neuronal factor contributing to post-exercise hypotension [19].

In the animal model, 'Central command' or its influence on vasomotor centers is augmented in hypertension. In spontaneously hypertensive rats, exaggerated renal SNS activity and pressor responses during spontaneously occurring motor activity are shown to be induced along a 'central command' pathway [20]. It is well known that regular exercise can benefit health by enhancing antioxidant defenses in the body. On the other hand, exhaustive exercise could generate excessive reactive oxygen species, leading to oxidative stress-related tissue damages and impaired muscle contractility [21]. Increased SNS activity is partly due to an imbalance between inhibitory and excitatory mechanisms within the PVN [7]. Adequate ExT in HF improves the altered inhibitory pathway utilizing nitric oxide [22] and GABA [23] mechanisms in PVN. Normalization of excitatory glutamatergic [24] and angiotensinergic [25] mechanisms within the PVN attenuates elevated SNS outflow in HF animal models with ExT [26].

In a human functional magnetic resonance imaging study, in addition to the traditional motor associated regions, Ic activation was associated with autonomic regulation during exercise, whereas decreased prefrontal cortex activation was observed during exercise at higher perceived intensities [27]. ExT improved the relationship between walking capacity and submaximal measure of cardiovascular fitness modulated by Ic integrity [28]. After ExT, the functional connectivity between Ic and amygdala was prolonged in an exercise intensity-dependent manner [29]. Thus, ExT is associated with improved the functional integrity of central autonomic network.

Increased wave reflex is recognized as a major hemodynamic finding of vascular aging, which is a determinant of central BP. In the PARAMETER (Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly) study, angiotensin receptor-neprilysin inhibitors were superior to AngII receptor blockers in reducing central systolic BP [30]. Aging vasculature generates an excess of the reactive oxygen species, superoxide and hydrogen peroxide, that compromise the vasodilatory activity of nitric oxide and facilitate the formation of the deleterious radical, peroxynitrite [31]. In the EnRicH trial, ExT significantly reduced AngII and central BP, and increased antioxidant effects, suggesting that ExT prevents the exacerbation of HF by reducing LV afterload equivalent to pharmacological treatment (Fig. 1).

In handgrip performance, the initial heart rate increase is primarily due to vagal withdrawal of parasympathetic activity [32]. It is also well known that higher exercise capacity is strongly associated with lower resting heart rate and indirect measures of high cardiac vagal activity, indicating that the parasympathetic nervous system plays a key role in optimizing exercise performance [33]. Despite the strong association between parasympathetic activity and exercise capacity, these data have long been interpreted as vagal activity merely being a marker for physical fitness. However, several lines of recent evidence obtained in studies of experimental animal models and human exercise support the hypothesis that the strength of cardiac vagal activity directly determines the individual ability to exercise [33].

The vagus nerve is a complex nervous system in the body, connecting vital organs such as the lungs, intestines, stomach, heart, and brain. Therefore, optimizing the

function of the vagus nerve is thought to ameliorate target organ damage. Tonic levels of aerobic exercise stimulate vagus nerve and lower stress responses. Exercise inhibited splenic TNF production through subdiaphragmatic vagus nerve [34]. The Xth cranial nerve has a cutaneous representation in the "Ramsay Hunt zone" located in the ear canal. Via Wrisberg's intermediate nerve, cutaneous stimuli reaches NTS which is the main brain area of integration for vagal afferents in brainstem [35]. In fact, distinct vagus evoked potentials were observed after stimulation inside the tragus [36].

Transcutaneous vagus nerve stimulation (tVNS) is a non-invasive, simple emergency treatment with few side effects that has spread worldwide by stimulation of the vagus nerve auricular branch of tragus [37–40]. tVNS has been reported to be effective in reducing SNS activity [37]. In HF with preserved ejection fraction, tVNS significantly improved LV [38], right ventricular performance [39], and renal congestion [39]. More recently, regarding for central BP, tVNS reduced LV afterload in acute HF patients [40].

Considering these results together, improving cardiovascular health with ExT might be a natural neuromodulation therapy that reduce LV afterload via autonomic regulation of the heart. These modulations are characterized by not only decreased SNS activity but also increased parasympathetic nervous system activity. To date, few studies have evaluated the impact of ExT on central BP in TRH. Therefore, the data presented in the study by Lopes et al. provide important implications for the prevention of worsening HF.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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