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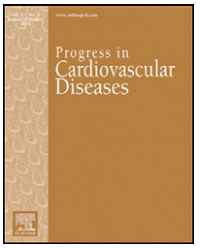

Exercise and Hypertension: Uncovering the Mechanisms of Vascular Control

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ABSTRACT

Hypertension (HTN) has recently been determined to be the number one overall risk factor of disease. With direct and indirect costs amounting to $46.4 billion in 2011 and projections of six-fold increases by 2030, the importance of low-cost nonpharmacological interventions can be appreciated. Vascular structural changes, endothelial dysfunction, and sympathetic overstimulation are major contributing factors to the pathophysiology of HTN. Exercise training (ET) for blood pressure (BP) control has been shown to be an effective and integral component of nonpharmacological interventions for BP control. Different ET modalities (aerobic, resistance, and concurrent training) have contributed differently to BP reduction and control, driving scientific discourse regarding the optimum ET prescription (modality, volume, and intensity) for such effects; ET results in a multitude of physiological effects, with vascular and autonomic adaptations providing major contributions to BP control. Despite widespread acceptance of the role and importance of ET for BP reduction, only 15% of US adults have been found to meet ET/physical activity recommendations. The purpose of this review is to explore BP lowering effects of aerobic and resistance ET and the underlying physiological mechanisms that result in such effects. Further research is required to enhance our understanding of the proper ET prescription for BP control across different age groups and racial ethnicities. Furthermore, research into methods of improving awareness and adherence to ET recommendations proves to be equally important.

Exercise and hypertension

It has been estimated that more than one in every three Americans have one or more types of cardiovascular disease (CVD), and nearly the same percentage have hypertension (HTN) (identified as systolic blood pressure [BP;SBP] ≥140 mmHg and/or diastolic BP [DBP] ≥90 mmHg or being on anti-HTN medication).[1] When considering pre-HTN (SBP ≥120 to<140 mmHg; DBP ≥80 to<90 mmHg), nearly 70% of Americans experience elevated BP.[1,2] About 17.3% of those with HTN are not aware of their condition,[1] and only half of those receiving treatment have their BP under effective control.[1] Given these current trends, it is thus not surprising that in 2010, HTN rose from the fourth to the overall number one global risk factor for disease.[3] HTN has been found to amount to the loss of five years of CVD-free life in adults

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Abbreviations and Acronyms

Ach = Acetylcholine

ANS = Autonomic nervous system

AT_1-R = Angiotensin II type 1 receptor

BP = Blood pressure

CHD = Coronary heart disease

CO = Cardiac output

CVD = Cardiovascular disease

DBP = Diastolic blood pressure

ET = Exercise training

FMD = Flow mediated dilation

HF = Heart failure

HTN = Hypertension of hypertensive

IMT = Intima medial thickness

MAP = Mean arterial pressure

NO = Nitric oxide

PEH = Post-exercise hypotension

SBP = Systolic blood pressure

SNS = Sympathetic nervous system

TPR = Total peripheral resistance

30–59 years of age.[4] In 2011, the direct and indirect cost of HTN was $46.4 billion, and projected to increase almost six fold by 2030.[1] With the association of such substantial risk across the lifespan, the importance of relatively low-cost nonpharmacological interventions can thus be further appreciated.

Both obesity[5] and physical inactivity,[6] ranked 6th and 10th overall risk factors for disease respectively,[3] play an important role in complicating CVD risk with HTN. The importance of exercise as a cornerstone treatment modality can be viewed in light of its ability to reduce the impact of a multitude of the top 10 CVD risk factors.

Across a wide range of etiologies, exercise training (ET) has previously been shown to rival and occasionally surpass, pharmacologic therapy in terms of treatment effectiveness for HTN.[7] In a recent meta-analysis of ET and drug trials on mortality outcomes,[8] there was no statistically significant difference between the two interventions in terms of mortality outcomes, excluding patients with stroke and heart failure (HF), where ET was determined to be more effective than drug interventions in terms of mortality reduction in the former population and was surpassed by diuretic drug therapies in the latter.[8] In patients with stable coronary heart disease (CHD), a 12-month ET program resulted in higher event-free survival rates than a standard percutaneous coronary intervention at nearly half the cost.[9]

Regarding HTN, aerobic ET has been shown to decrease BP by 5–7 mmHg while resistance ET leads to a 2–3 mmHg decrease.[2] Reductions of the magnitude found with aerobic ET translate to a decrease in the risk of stroke by 14%, CHD by 9%, and total mortality by 7% (6%, 4%, 3% for resistance ET, respectively).[10] Aerobic ET has been widely accepted and recommended as the first line of treatment for BP reduction and control both nationally and internationally.[11–17] Even as well-established evidence favoring the benefits of ET on BP continues to grow, only 15% of US adults have been reported to meet ET recommendations and therefore a substantial number of adults are at risk of poor BP control.[18]

Unlike aerobic ET, the role of resistance ET with respect to BP lowering effects and whether or not it can be used as the primary intervention for BP lowering and control is less clear. This review will summarize current literature regarding the effects of different ET modalities and proposed physiological mechanisms of BP lowering in response to various exertional stimuli.

Aerobic ET and BP

Aerobic ET has been determined to have both acute and chronic effects on BP. Fitzgerald[19] was the first to describe the term post-exercise hypotension (PEH), which later became the tenant of acute physiological effects of ET on BP. This drop in BP post exercise has also been found to be dose-dependent,[20] with higher intensity ET resulting in greater reductions in BP. This observation can be further confirmed by results of a recent meta-anlysis[21] showing a dose–response relationship between aerobic ET intensity and improved endothelial function measured by flow-mediated dilation (FMD). Increased endothelial function is associated with and may contribute to lower peripheral vascular resistance. The magnitude of the BP drop has also been found to depend on pre-exercise BP.[12] People with higher baseline BP readings show greater PEH compared to normotensives. It was also shown that people with higher baseline BP readings show the greatest reductions after chronic ET.[22] PEH has been demonstrated to be effective and significant in patients receiving anti-HTN medication after a single bout of ET,[23] and has been found to be effective across all age groups, including those 80–90 years of age.[24] In patients with resistant HTN, defined as those unable to reach target BP readings despite receiving 3 or more anti-HTN medications one of which being a diuretic,[25] a treadmill walking protocol of 3×/week for 8–12 weeks at an intensity slightly above aerobic threshold was successful in reducing systolic and diastolic 24-h ambulatory BP by 6 ± 12 mmHg and 3 ± 7 mmHg, respectively.[25] Interestingly, the finding that PEH can occur effectively after ET durations as short as 15 minutes at low intensity (40% VO_{2peak}), in contrast to high-intensity interval ET,[26] is likely very clinically relevant to HTN individuals unable to perform long bouts of ET.[27] When compared to a single 30-min ET bout, three 10-min bouts at 60%–65% VO_{2peak}were shown to be equally effective in lowering 24-h ambulatory SBP.[28] Furthermore, in a randomized crossover trial,[29] 10-min exercise bouts of treadmill walking at 50% VO_{2peak} performed once an hour over four hours showed equivalent BP reductions to a single 40-min exercise session and lasted longer (up to 3 hours) before returning to baseline[29]; BP was reduced for approximately 10 hours in the group receiving intermittently accumulated ET compared to 7 hours for the continuous ET group.

Nonetheless, it was previously identified that nearly 24% of people with elevated BP do not show reductions in BP post exercise.[30]A study by Liu et al,[31] showed strong correlations ($r = 0.89$, $P < 0.01$) between acute and chronic BP reduction responses. Participants who demonstrated the greatest BP reductions to acute exercise had the greatest chronic

reductions post 8-weeks of aerobic ET.[31] It was thus suggested that PEH can be utilized as a screening tool to estimate the prognostic benefits of ET on an individual basis and guide treatment modality selection.[2,31] Utilizing PEH clinically has contributed to the recommendation of aerobic ET on most and preferably all days of the week.[2,11,12,14,15,32]

Resistance ET and BP

Unlike aerobic ET, resistance ET studies have shown much more conflicting results.[12,33–36] In a recent meta-analysis[22] comparing the effects of different ET modalities (endurance, dynamic resistance, concurrent training [combined endurance and resistance training], and isometric training) on BP, endurance ET, dynamic resistance ET and isometric ET were all found to significantly lower SBP (–3.5 mmHg, –1.8 mmHg, and –10.9 mmHg, respectively) and DBP (–2.5 mmHg, –3.2 mmHg, and –6.2 mmHg, respectively). Concurrent training was only found to significantly reduce DBP (–2.2 mmHg) but not SBP. The authors reported no significant differences between endurance, resistance, and isometric ET on SBP or DBP. Of note was their subgroup analysis showing BP reductions after endurance ET were more pronounced in males and HTN participants, while groups of participants with pre-HTN showed greatest reductions with dynamic resistance training.[22] This observation may have significant clinical significance regarding ET prescription if these findings are confirmed by future investigations.

Moraes et al[37] studied the effects of 12-weeks conventional resistance ET at 60% 1-repetition maximum (1-RM) on BP in middle-aged men with stage-1 HTN. All participants terminated pharmacological treatment and went through a 4-week washout period. Post-training results show mean SBP reductions of 16 mmHg and mean DBP reductions of 12 mmHg.[37] The authors also showed that SBP reductions became significant in week 2 of training while DBP reductions only became significant during the last two weeks of training. SBP reductions reported in this study are in line with a recent controlled study in elderly women with HTN (pharmacologically controlled).[38] Four months of resistance ET resulted in mean SBP reductions of 14.3 mmHg compared to baseline. DBP was reduced by 3.8 mmHg but found not to be statistically significant when compared to baseline. Participants underwent 1-month adaptation exercises at low-intensity, then at 60%, 70%, and 80% of 1-RM for each ensuing month. Moraes et al[37] also reported BP measures during and after a 4-week detraining period and were able to show maintenance of post-training BP reductions during the whole detraining period. BP reductions following ET have been shown to maintain a significant reduction for up to 14-weeks post-training[39] and may thus hold compelling clinical utility.

Collier et al[40] compared the effects of 4-weeks aerobic and resistance ET on hemodynamics and arterial stiffness in individuals 30–60 years of age with pre and stage-1 HTN, not receiving any medication. Results show that both treatment groups decreased SBP and DBP (–4.6 mmHg, –3.1 mmHg, respectively). However, participants undergoing resistance ET also showed significant increases in arterial stiffness, a marker that has been associated with increased risk for HTN.[41] However, this increase in stiffness was counterbalanced by greater increases in peak forearm blood flow and vascular conductance with resistance ET compared to aerobic ET (52% vs. 19%). These results suggest: 1) resistance ET can be as effective as endurance ET for BP reduction; and 2) underlying physiological mechanisms responsible for BP reductions may be different between ET modalities.

The effects of acute resistance exercise on hemodynamics differ between sedentary untrained individuals and trained individuals.[42,43] Sedentary individuals have been shown to have decreased endothelium-dependent vasodilation, measured by FMD, in response to acute HTN (>170 mmHg) induced by strenuous resistance exercise.[43,44] However, both endurance trained athletes and conditioned weightlifters alike show improved FMD responses to acute resistance exercise.[43] Reduction in FMD in response to acute resistance exercise appears to be independent of body mass. Franklin et al[45] reported improved acute FMD after eight weeks of circuit weight training in young obese, otherwise healthy, young women in the absence of weight loss. Altogether, these data suggest that aerobic ET and resistance ET can both provide protection against impaired endothelial function in response to acute HTN. In contrast to aerobic ET, endothelial responses to resistance ET have been found not to follow a dose-dependent relationship but rather a frequency-dependent association.[21]

Mechanisms of BP reduction

Multiple mechanisms contribute to the adaptations of BP to ET. Given that mean arterial pressure (MAP) is governed by cardiac output (CO) and total peripheral resistance (TPR), changes in one or both of these variables need to be examined.[12,46] Although ET has been known to affect both stroke volume and heart rate (determinants of CO), net CO has been shown not to change, or increase slightly, with ET.[46,47] This would leave TPR as the primary determinate of MAP change as a result of ET. Peripheral resistance may be modulated through changes in vascular function or structure following ET. Fig 1 summarizes the different effects of aerobic and resistance ET on BP.

ET preserves and enhances vascular function

Vascular function has been shown to be mediated by multiple neurohormonal control mechanisms.[47–49] Endothelial dysfunction has become the hallmark of local vascular function impairments in patients with HTN and those with poor CVD risk profiles[7,48–51]; evidence points to nitric oxide (NO) bioavailability as the main contributor to this dysfunction in both large and small blood vessels.[48,49] NO bioavailability can be modulated via different physiological stimuli (e.g., upregulated by exercise and dietary factors; and downregulated by oxidative stress and modified low-density lipoproteins).[49,52] In addition, physical inactivity has been associated with downregulation of NO bioavailability and increased oxidative stress.[53] In isolated resistance vessels extracted from adipose tissue,[54] exposure to transient elevations in intraluminal

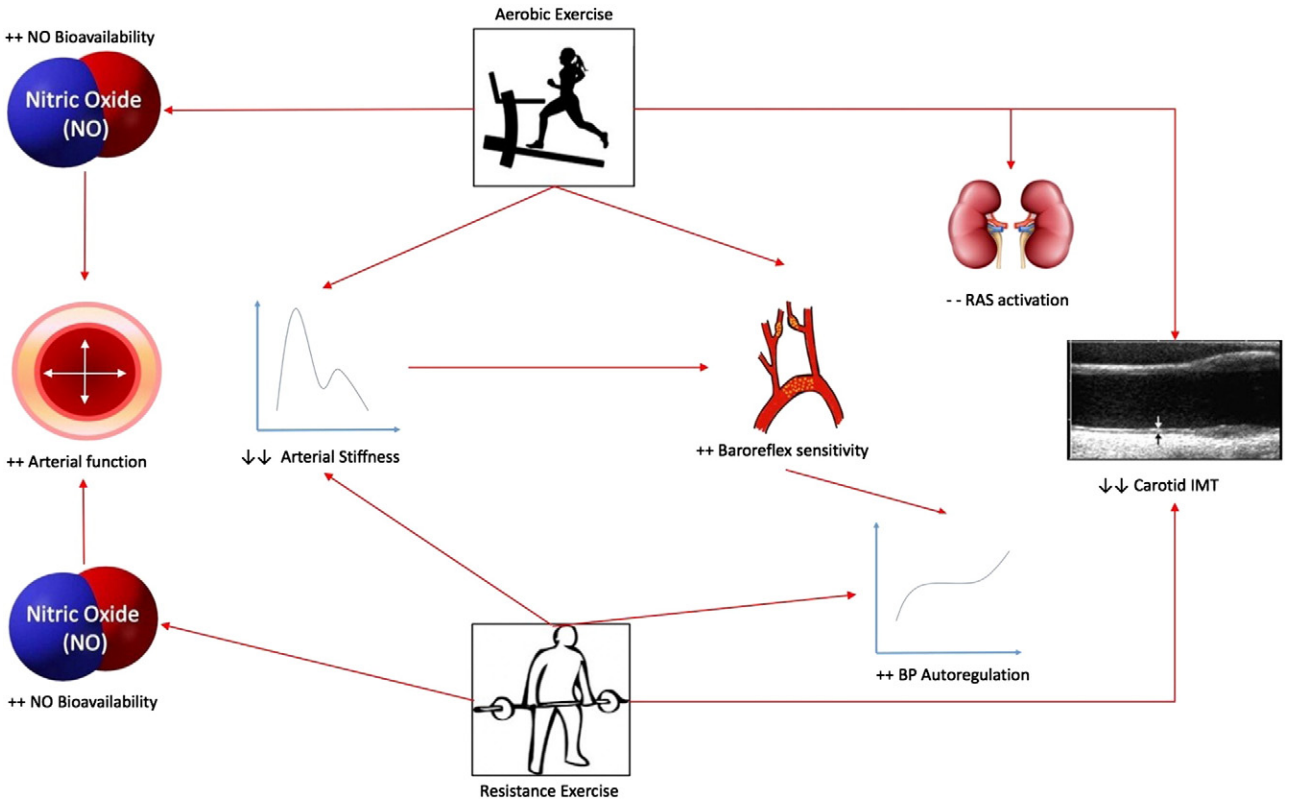

Fig 1 – The effect of aerobic and resistance exercise on arterial structure and function. Abbreviations - RAS: renin-angiotensin system; IMT: intra-media thickness; BP: blood pressure; NO: nitric oxide.

pressure to 150 mmHg was found to blunt vascular responsiveness to acetylcholine (ACh) suggesting a direct effect of BP on endothelial function.[48] A 30-min exposure to intraluminal pressure of 150 mmHg resulted in significant elevations in superoxide anion levels,[54] a scavenger of NO.[49] As discussed earlier, endothelial dysfunction as a result of acute BP elevations has been observed in sedentary individuals after acute resistance ET[42,43]; however, chronic resistance ET was shown to maintain and enhance endothelial function.[42,43,55] The exact mechanisms require further investigation but possible explanations include increases in shear stress, improved expression and activation of endothelial NO synthase, improved vascular antioxidant capacity, and improved superoxide dismutase expression and activity.[42,56] Although endothelial dysfunction is a predictor of HTN and other CVD events,[57,58] these data also suggest that high BP can further exacerbate endothelial dysfunction.

In addition to reduced NO bioavailability and poor vasodilatory ability, patients with HTN also exhibit increased vasoconstrictor tone.[54] Both the vascular and systemic renin-angiotensin system have been determined to contribute to increased vasoconstrictor tone.[54,59] ET has been shown, in addition to improving vasodilatory function, to decrease vasoconstrictor tone, mainly through decreasing endothelin-1 endogenous bioavailability.[60] In a randomized controlled trial, Adams et al[59] demonstrated that four weeks of ET lead to a decrease in mRNA and protein expression of the angiotensin II type 1 receptor (AT_1-R), which is necessary for the vasoconstrictive effect of angiotensin II. In addition, another study found losartan, the AT1-R blocker, was able to block the acute effects of elevated BP (similar to that which occurs during acute resistance ET) on lowering endothelium-dependent vasodilation to ACh.[54] These data suggest that ET may modulate the local effects of exercise on local RAS components that may alter vascular function and promote HTN.

ET alters vascular structure

Chronic ET, both aerobic and resistance, have also been shown to impact vascular structure. Spence et al[61] studied the effects of 6-months of endurance and resistance ET on arterial structure and function. Their results indicated a local effect of ET, as the resistance ET group, which predominantly performed upper extremity exercises including hand gripping, showed improved brachial artery FMD and resting diameter that were absent in the femoral artery.[61] Evidently, the aerobic training group predominantly performed lower extremity exercises. Results from the aerobic ET group showed improved femoral artery FMD and resting diameter that were absent in the brachial artery of these subjects, indicating a local effect of ET.[61] Both groups showed a decrease in carotid artery intima-media thickness (IMT),[61] a measure of arterial structure. Carotid IMT is a strong predictor of CVD events.[62] An absolute carotid IMT increase of 0.1 mm is predictive of age and sex-adjusted risk of future myocardial infarction by 10%–15% and stroke by 13%–18%.[62] Taken together, these results support a local effect of ET on *conduit artery diameter* rather than a systemic effect. Findings of such nature have

been previously reported.[63,64] However, these findings are different from the systemic improvements in *arterial function* that have been widely reported with ET.[65,66]

A tradeoff between structure and function?

Laughlin[67] previously hypothesized that improvements in endothelial function in response to acute ET may act to normalize increases in shear stress until structural remodeling ensues, after which endothelial function returns to near baseline values.[7,68] This hypothesis was supported by Tinken et al[68] Brachial and popliteal artery structure and function were assessed on a bi-weekly basis throughout an 8-week ET program.[68] Interestingly, arterial function peaked at week 2 for both arteries, and slowly declined to near baseline levels by the end of the training period. On the other hand, arterial structure, measured by vasodilatory capacity,[68,69] continued to increase progressively throughout the 8-week ET program. This notion is further supported by the observation of an inverse relationship between artery diameter and FMD,[70] and provides important insight into the adaptation of the vasculature to ET.

Exercise and arterial stiffness

Arterial stiffness has long been considered a major risk factor for age-related morbidity and mortality.[41,71] Large elastic arteries, like the aorta and carotids, play a major role in buffering pressure fluctuations on a beat-to-beat basis[41,71] and prevent significant pulsatile fluctuations. Furthermore, reduced arterial compliance may increase aortic impedance and left ventricular afterload[72] and contribute to reduced exercise capacity,[73] left ventricular hypertrophy, and HF.[74] Tanaka et al[73] observed a 25% increase in arterial compliance and a 20% reduction in β-stiffness, a measure of arterial stiffness, of the carotid artery after 3-months of aerobic ET in middle-aged and older men. These improvements were sufficient to normalize arterial compliance with middle-aged/older endurance athletes.[73] In addition to previously mentioned benefits, increases in arterial compliance have been associated with improved arterial baroreflex sensitivity and BP.[75,76] Surprisingly, in elderly patients with HTN, studies evaluating arterial stiffness changes with aerobic ET have yielded inconsistent results. Acute maximal exercise in elderly participants with HTN[77] improved arterial compliance and β-stiffness with concomitant lowering of DBP and MAP. After 20-weeks of aerobic ET at a heart rate representing 70% VO_{2max}, arterial stiffness indices remained unchanged compared to baseline values.[77] Trends in reduced DBP and MAP were evident but did not reach statistical significance. Similar results regarding unimproved arterial stiffness were reported following 8-weeks of aerobic ET at 65% of predetermined maximum heart rate in patients with isolated systolic HTN.[78] Similarly, SBP and DBP were unchanged between treatment and control groups.[78] These results suggest that arterial stiffness changes precede and may predict BP changes following exercise interventions. Further investigation into the effects of exercise on arterial stiffness in elderly patients and those with established CVD appears warranted.

Resistance ET has been associated in the literature with increases in arterial stiffness[40,71,79,80]; however, most of these studies were performed in young normotensive individuals utilizing high-intensity ET regimens.[72] Thirteen weeks of strength training, 3-days/week at 70% 1-RM, in middle-aged and older individuals did not result in increases in arterial stiffness despite increases in 1-RM by 25%–35%.[81] Interestingly, BP did not change following this intervention.[81]

The extent to which increases in arterial stiffness following resistance ET effect BP is a question that remains to be answered. Studies by Collier et al[80] have provided some insight into reported increases in arterial stiffness post-resistance training in men with pre to stage 1 HTN; however, SBP was significantly reduced. This finding could be explained by the observation of increased forearm blood flow following resistance training in the same group.[80] Furthermore, female participants did not show increases in arterial stiffness after resistance ET but did show greater SBP and DBP reductions compared to aerobic ET.[80] Collectively, these findings suggest: 1) resistance ET may lower BP despite increases in arterial stiffness; 2) resistance ET may prove to be a more favorable treatment modality for women with HTN and in African Americans susceptible to HTN.

ET and the autonomic nervous system (ANS)

BP control is governed by multiple physiological systems, the ANS being one of them.[82] Overstimulation of the sympathetic nervous system (SNS), loss of cardiac parasympathetic control and increased angiotensin II activity have been observed and well documented in patients with HTN.[12,83] The effect of the SNS on the vasculature is that of systemic vasoconstriction and increased TPR, leading to an increase in BP. The arterial baroreceptors in the aortic arch and carotid sinus play crucial roles in monitoring BP changes and responding accordingly.[84] Increased sensitivity of these baroreceptors has been observed in patients with HTN.[31,85] ET can modulate and normalize the SNS overactivity observed in patients with HTN and reset baroreflex sensitivity.[12,82,86] Laterza et al[85] demonstrated that three 60-min ET sessions/week performed at 70% peak VO_2 for 4-months in patients with HTN were successful in reducing SBP, DBP, muscle sympathetic nerve activity as well as restoring baroreflex sensitivity back to normotensive control levels. Furthermore, similar BP reduction results and improved autonomic regulation measured by heart rate variability were found in patients with HTN after 8-weeks of inspiratory muscle training.[87]

It has been suggested that improvements in baroreflex sensitivity as a result of ET may be due to a mechanical or a neural component. Mechanically, improved arterial compliance and distensibility may improve sensitivity of arterial baroreceptors and enhance stimulus transduction.[76,86] Deley et al[88] tested the contribution of both components to enhanced baroreflex sensitivity after 6-months of aerobic ET in healthy, previously sedentary, older individuals. The authors reported improvements in both components; however, only the neural component was directly associated with the ET stimulus. Altogether, the effects of ET on ANS regulation tend to indicate that exercise training reduces

SNS activity and improves baroreceptor activity. More studies need to be performed in the HTN population to better understand the interrelationships between ET, ANS and HTN.

Conclusions

The added health risks attributed to HTN have been widely accepted. The efficacy of ET, especially aerobic ET, in terms of BP reductions has also been widely accepted and appreciated. However, this acknowledgment of exercise efficacy and importance has not always translated into clinical application. Furthermore, only 15% of US adults have been reported to meet current ET recommendations.[18] With significant BP-lowering effects after ET lasting from 3 to 10 minutes in duration, this level of adherence is indeed disconcerting. Understanding interventions that promote the prescription and adherence of ET recommendations across populations as a first line of defense for BP reduction and the prevention of HTN is a critical area for future research. In addition, further investigation is needed to determine exact dosage and preferred modes of ET across different populations in order to promote individualized and optimally effective ET prescription. As discussed previously in this journal, a call to action for ET across the healthcare system and globally is needed,[89–91] as a cost-effective strategy,[92] for the prevention and treatment of many chronic diseases, including CVD in general and HTN specifically.

Statement of Conflict of Interest

None of the authors have any conflicts of interests with regard to this publication.

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