Isometric Handgrip Effects on Hypertension

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Abstract: Hypertension is estimated to affect 1 billion people worldwide, and is associated with an increased risk of cardiovascular disease and all-cause mortality. The management of high blood pressure focuses on lifestyle modifications (i.e. diet, exercise, smoking cessation) and drug therapies. Despite these strategies, many patients are still unable to maintain or control their blood pressure within desired levels. Recent research has identified isometric handgrip (IHG) training as a potential therapeutic modality. Results demonstrate a hypotensive effect of IHG training in medicated and unmedicated patients. This novel therapy may be efficacious based on low associated costs and time requirements (33 min/week). The mechanisms coupled with the attenuations in resting blood pressure remain contentious. However, recent evidence has begun to suggest that beneficial modulation of the autonomic nervous system is responsible for the positive changes in blood pressure. While further IHG research is required, the prospect of a novel non-pharmacological therapy for hypertension has major public health implications. This review will summarize the previous literature, discuss future research directions, and describe clinical significance.

Key Words: Blood pressure, hypertension, isometric exercise.

INTRODUCTION

Hypertension (HTN) is one of the most prevalent and powerful risk factors for cardiovascular disease. It is estimated to affect nearly one quarter of the adult population, and results in 7.1 million deaths each year [1, 2]. Further discouraging is the prospect that the prevalence of HTN is projected to increase 60% by 2025 [3]. Recent research from the Framingham Heart Study has shown that the residual lifetime risk for developing HTN in healthy middle-aged and elderly individuals is 90% [4]. The consequence of these statistics is a concerted global effort towards the primary, secondary, and tertiary prevention of HTN [1, 2].

It is undeniable that the treatment of HTN reduces the risk of cardiovascular disease, cerebrovascular disease, and mortality [1]. The first-line therapy for HTN should consist of lifestyle modifications (i.e. exercise, diet, smoking cessation, etc) aimed at reducing HTN risk factors. However, the current mainstream therapy for HTN is the prescription of anti-hypertensive medications. Poor effectiveness and adherence to these prescriptions has resulted in low rates of blood pressure control [5]. Moreover, research has demonstrated that ~50% of HTN patients may still maintain elevated resting arterial blood pressure (ABP) [6].

Thus, the ineffectiveness of HTN therapies has necessitated the need to investigate novel therapeutic alternatives. The interest in isometric handgrip (IHG) training as a potential HTN therapy has increased following the results of numerous studies demonstrating hypotensive effects with training. This review will focus on the effects of IHG training on resting ABP, the potential mechanisms responsible for these attenuations, and the clinical significance of this potential therapy. Future directions for research will also be highlighted.

ISOMETRIC EXERCISE

Isometric or static contractions differ from dynamic movements as they contain an application of force but no change in muscle length. Early research in the area of isometric exercise focused on the differences between isometric and dynamic exercise [7, 8]. One key difference is the initiation of the metaboreflex in an attempt to restore blood flow, since isometric contractions impair blood flow even at low intensity levels (~20% maximum voluntary contraction (MVC)) [9, 10]. A second more controversial aspect is the cardiovascular response to isometric exercise, often cited as proof for its opposition in special populations. The blood pressure and heart rate responses to isometric exercise are influenced by the force of the contraction [11], the size of the contracting muscle [12] and the length of time contracted [13]. Similar to strength exercise, the cardiovascular response is characterized by an increase in cardiac output and ABP, resulting in a pressure load on the heart with little change in total peripheral resistance [14]. With respect to IHG exercise, which is commonly performed at ~30% of MVC, research has shown only modest increases in ABP and heart rate with a 2-minute contraction [7]. In comparison to dynamic exercise (exhausting treadmill-walking protocol), sustained handgrip contractions elicited lower systolic blood pressure and heart rate responses [7]. Thus in patients recommended for traditional exercise therapies, low intensity isometric exercise (< 30% MVC) is well tolerated and acceptable.

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ISOMETRIC HANDGRIP TRAINING

The interest in isometric exercise as a means to lower resting ABP stems from two landmark studies. The first, conducted by Kiveloff and Huber (1971) demonstrated that total body isometric contractions decreased resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) in hypertensive individuals [15]. The second, an epidemiological study conducted by Buck and Donner (1985) found that in a sample of 4,273 men, moderate or heavy occupational isometric exercise was associated with a reduced incidence of hypertension [16]. Surprisingly, since these two early studies only a handful of published research has investigated the hypotensive effects of isometric activity.

In the first series of investigations utilizing handgrip dynamometers (similar to the one seen in Fig. **1**), Wiley and colleagues (1992) developed and investigated two isometric handgrip protocols [17]. In the first protocol, participants with high-normal DBP trained 3d.wk⁻¹ for 8-weeks, completing four 2-minute contractions at 30% MVC, separated by 3-minute rest periods. Training resulted in a decrease in SBP by 13 mmHg and DBP by 15 mmHg. In the second protocol, borderline hypertensive participants completed four 45-second contractions at 50% MVC, separated by 1-minute rest periods 5d.wk⁻¹ for 5-weeks. Training resulted in a decrease in resting SBP by 10 mmHg and DBP by 9 mmHg.

Fig. (1). Digital isometric handgrip trainer (Image used with permission of Zona Health).

Since the original IHG investigations conducted by Wiley *et al.* (1992) [17], a number of studies have demonstrated a reduction in resting ABP with IHG training. In one randomized control trial, Taylor *et al.* (2003) extended the training time to 10 weeks and sampled medicated hypertensive participants (SBP: 156 ± 9 mmHg, DBP: 82 ± 9 mmHg) [18]. In the training group, SBP decreased by 19 mmHg, DBP by 7 mmHg and MAP by 11 mmHg. Of concern, the control group in this study also had reductions in SBP, DBP and MAP of 8 mmHg, 3 mmHg, and 5 mmHg, respectively. This demonstrates the need for well controlled familiarization sessions and the potential influence of confounding factors, such as stress-related modulations on resting ABP.

Similarly, a reduction in resting ABP was replicated by McGowan and associates (2007) [19]. Medicated HTN participants were randomized to either bilateral or unilateral IHG training. Following the 8-week IHG protocol, bilateral training decreased SBP from 134 ± 5.0 mmHg to 119 ± 4.0 mmHg, while unilateral training reduced SBP from 142 ± 4 mmHg to 132 ± 4 mmHg. To date, this is the only study to compare bilateral and unilateral training protocols. Further study is needed to establish any associated differences in attenuation magnitude between these protocols.

Peters *et al.* (2006) recently repeated one of the original [17] training protocols (4 contractions at 50% MVC, 5d. wk⁻¹) in newly diagnosed unmedicated hypertensives [20]. After 6-weeks of training, results show a larger reduction in SBP compared to the first study to utilize this protocol [17] (13 mmHg versus 9.5 mmHg, respectively). The difference in IHG training effects between these studies may be a result of initial baseline SBP discrepancies. There is statistical evidence that individuals with higher baseline SBP levels illustrate greater rates of attenuation in resting ABP with IHG training [21].

Ray and Carrasco (2000) conducted the first IHG training study on young normotensive participants [22]. The training group performed four 3-min contractions at 30% MVC, 4d.wk⁻¹ for 5 weeks. Resting DBP and MAP significantly decreased in the trained group, while SBP did not change. The lack of change in SBP and the small changes in DBP and MAP (reduction of 5 mmHg and 4 mmHg respectively) were most likely due to the fact that participants were normotensive, unlike previous IHG training studies where the participants had elevated resting ABP.

Our laboratory has since undertaken an 8-week IHG study utilizing inexpensive spring handgrips [23], rather than the hand dynamometers used in prior investigations [17-22]. In contrast to previous studies, this randomized controlled trial sampled normotensive, unmedicated participants. The final effect of IHG training was significant reductions in both SBP (122 ± 3 mmHg to 112 ± 3 mmHg, p<0.01) and DBP (70 ± 1 mmHg to 67 ± 1 mmHg, p<0.05), with no change in control participants. Longitudinal analysis revealed more conservative reductions of 5 mmHg and 1 mmHg for SBP and DBP, respectively. Of interest to the reader, this study noted pre-post reductions in 23 out of 24 training participants [23].

In addition, we recently completed a summative analysis of three IHG training studies completed in our laboratory [21]. Participants (*n*=43) were medicated hypertensives who had completed the same training protocol (30% MVC, 3d.wk⁻¹). As a novel aspect, we completed longitudinal analysis using hierarchical linear modeling (HLM). With HLM we were able to examine changes in resting ABP over time, avoiding the limitations of a pre-post design. Longitudinal HLM analysis revealed a reduction in SBP and DBP of 5.7 and 3.0 mmHg, respectively, over the course of the 8-week training protocols. In comparison, pre-post analysis demonstrated reductions in SBP and DBP of 4 mmHg and 2 mmHg, respectively. An important result from this study was the large correlation between high baseline SBP and greater

attenuations in resting ABP (r = -0.67) [21]. These results highlight the beneficial effects of IHG and the inconsistencies of only using pre-post analysis with longitudinal cardiovascular studies. Table **1** summarizes the details and outcomes of the investigations discussed in this section.

MECHANISMS RESPONSIBLE FOR IHG ATTENUATIONS

While these recent IHG studies have consistently demonstrated hypotensive effects, the mechanism(s) responsible for these attenuations continue to elude investigators. Due to the lack of research in this area, only a handful of hypothesized mechanisms have been investigated. In addition, the difference in sample populations has made comparison of current results difficult. Nonetheless, current mechanistic IHG research has focused mainly on systemic adaptations with training.

IMPROVED OXIDATIVE STRESS

The generation of reactive oxygen species in excess of cellular antioxidant capacity is thought to play a critical role in vascular damage and the pathophysiology of HTN [24-26]. Research on HTN patients has demonstrated increased production of superoxide anions, reduced synthesis of nitric oxide, and decreased bioavailability of antioxidants [27, 28]. To date, only one study has examined the effects of IHG training on markers of oxidative stress [20]. Peters *et al.* (2006) reported a significant reduction in exercise-induced oxygen centred radicals (-266%), with an accompanying

Table 1.   Effects of Isometric Handgrip (IHG) Training on Resting Arterial Blood Pressure

Reference	Design	IHG Protocol	Participants	Findings
Wiley *et al.* 1992 [a]	Prospective cohort	3d.wk^{-1} for 8-weeks, 30% MVC	High-normal DBP (*n* = 8, ages 20-35)	↓ SBP 13 mmHg ↓ DBP 15 mmHg
Wiley *et al.* 1992 [a]	Longitudinal cohort	5d.wk^{-1} for 5-weeks, 50% MVC	Borderline hypertensives (*n* = 10, ages 29-52)	↓ SBP 10 mmHg ↓ DBP 9 mmHg
Ray and Carrasco 2000 [b]	RCT	4d.wk^{-1} for 5-weeks, 30% MVC	Unmedicated normotensives (*n* = 24 , ages 19-35)	↓ DBP 5 mmHg ↓ MAP 4 mmHg
Taylor *et al.* 2003 [c]	RCT	3d.wk^{-1} for 8-weeks, 30% MVC	Medicated hypertensives (*n* = 17, mean age: 67)	↓ SBP 19 mmHg ↓ DBP 7 mmHg ↓ MAP 11 mmHg
Peters *et al.* 2006 [d]	Longitudinal cohort	5d.wk^{-1} for 6-weeks, 50% MVC	Unmedicated hypertensives (*n* = 10, mean age: 52)	↓ SBP 13 mmHg
McGowan *et al.* 2007 [e]	Longitudinal cohort	3d.wk^{-1} for 8-weeks, 30% MVC	Medicated hypertensives Bilateral: (*n* = 7, mean age: 62) Unilateral: (*n* = 9, mean age: 66)	Bilateral IHG training: ↓ SBP 15 mmHg Unilateral IHG training: ↓ SBP 10 mmHg
Millar *et al.* 2007 [f]	Meta-analysis 3 studies	3d.wk^{-1} for 8-weeks, 30% MVC	Medicated hypertensives (*n* = 43, ages 38-77)	Longitudinal analysis: ↓ SBP 6 mmHg ↓ DBP 3 mmHg Pre-Post analysis: ↓ SBP 4 mmHg ↓ DBP 2 mmHg
Millar *et al.* 2008 [g]	RCT *Spring handgrips	3d.wk^{-1} for 8-weeks, 30% MVC	Unmedicated normotensives (*n* = 49, mean age: 66)	Longitudinal analysis: ↓ SBP 5 mmHg ↓ DBP 1 mmHg Pre-Post analysis: ↓ SBP 10 mmHg ↓ DBP 3 mmHg

DBP, diastolic blood pressure; MAP, mean arterial pressure; MVC, maximal voluntary contraction; RCT, randomized control trial; SBP, systolic blood pressure.

a, [17]; b, [22]; c, [18]; d, [20]; e, [19]; f, [21]; g, [23].

increase in the ratio of resting whole blood glutathione to oxidized glutathione (+61%). As mentioned previously, training participants demonstrated a significant reduction in SBP (13 mmHg) [20]. Increased antioxidant production may therefore be a mechanism responsible for the hypotensive effects of IHG training. These results hint at the potential improvement in endothelium-dependent dilation through increased nitric oxide availability due to reduced oxidative stress.

IMPROVED ENDOTHELIAL FUNCTION

HTN is associated with endothelial dysfunction, characterized by reduced vasodilation, pro-inflammation, and pro-thrombotic properties in the vasculature [29]. One cause for this dysfunction is the reduction in formation and/or bioavailability of nitric oxide, a potent endothelium derived vasodilator. One postulated mechanism thought to be responsible for attenuations in resting ABP with IHG training is improved endothelium-dependent vasodilation. To this end, Katz *et al*. (1997) [30] and Hornig *et al*. (1996) [31] investigated the effects of rhythmic handgrip training on endothelial function in individuals with endothelial dysfunction. Both protocols required participants to perform 20 contractions per minute for 30 minutes each day for 8 and 4 weeks, respectively. A localized improvement in endothelial-dependent vasodilation but not endothelial-independent vasodilation was found in both studies [30, 31].

The improvement in endothelial-dependent vasodilation with rhythmic handgrip training led McGowan and colleagues [19, 32] to investigate whether these results may be responsible for the reduction in resting ABP with IHG training [17-22]. It was hypothesized that the increase in heart rate and ABP with IHG training were sufficient to increase systemic pulsatile blood flow, leading to improvements in systemic vasodilation [18, 22]. McGowan *et al*. (2006) examined the effects of bilateral and unilateral IHG training protocols on endothelial-dependent vasodilation and resting ABP in medicated HTN patients [32]. They demonstrated that the bilateral IHG training improved brachial artery (BA) flow-mediated dilation (FMD) in both arms; in contrast, unilateral training only improved BA FMD in the trained arm. However, a similar study of normotensive participants found no significant changes in BA FMD following 8-weeks of unilateral IHG training [33]. Therefore, the improvements in local endothelial-dependent vasodilation alone, lead the authors to conclude that a systemic improvement in endothelial dysfunction is not a likely mechanism for the hypotensive effect of IHG training.

The local improvement in endothelial-dependent vasodilation may be a result of an increase in nitric oxide bioavailability due to shear stress, improved antioxidant activity and/or enhanced endothelium-independent vasodilation [19]. A recent study examined the role of smooth muscle vasodilation on improvements in BA FMD following 8 weeks of IHG training [32]. These results demonstrate enhanced BA FMD with IHG training but no change in nitroglycerin-mediated maximal vasodilation (an index of endothelium-independent vasodilation) in the trained arm. The local improvements in BA FMD are therefore not a result of underlying changes in the forearm vasculature [32]. As a result of these studies, it is unlikely that improved endothelium-dependent and/or endothelium-independent vasodilations are the primary mechanisms responsible for the attenuations in ABP observed with IHG training.

IMPROVED AUTONOMIC FUNCTION

HTN is also associated with negative changes in sympathovagal balance [34], predominantly through excessive sympathatetic activity [35]. Sinoway *et al*. (1996) [36] and Somers *et al*. (1992) [37] examined the effect of forearm endurance training on sympathetic nerve responses. Both studies found that endurance forearm training significantly attenuated the increase in the sympathetic nerve response [36, 37]. These results led investigators to hypothesize alterations in autonomic nervous system (ANS) activity as a possible mechanism for the hypotensive effect following IHG training. Taylor and colleagues (2003) investigated this hypothesis and found changes in ANS activity, which may contribute to the hypotensive effect of IHG training [18]. As mentioned previously, reductions in SBP and MAP were found in the training group. Power spectral analysis of heart rate variability and blood pressure variability was used to evaluate changes in modulation of the ANS. Heart rate and blood pressure variability analyses revealed decreased sympathetic and increased vagal activity, represented by a significant decrease in low frequency area and an increase in high frequency area, respectively [18]. In contrast, Ray and Carrasco (2000) measured pre-post muscle sympathetic nerve activity (MSNA) in the peroneal nerve. They observed no significant changes in MSNA (14 ± 2 to 15 ± 2 bursts/min). While this finding is opposing to HRV results, it must be remembered that this study engaged young normotensive subjects and had very modest reductions in ABP [22]. Nonetheless, a beneficial shift in autonomic modulation could explain the reductions in resting ABP after IHG training.

More recently, our laboratory has begun to investigate the effects of a single acute bout of IHG on sympathovagal balance. In contrast to traditional linear analysis of heart rate variability with power spectral methodology, our research has utilized non-linear analysis of heart rate complexity. This technique may provide additional information regarding subtle changes in sympathovagal balance, which may not be detected by linear methods. Sample entropy was used as our measure of heart rate complexity. Complexity measures assess the randomness of patterns within a time-event series, which is a reflection of both sympathetic and parasympathetic contributions [38]. In this context, numbers approaching 2 are considered "more random" and linked with parasympathetic activity, while numbers approaching 0 are considered "less random" and linked with sympathetic activity. As seen in Fig. **2**, unpublished preliminary results demonstrate a potential dose-response of sympathetic stimulation during each of the four 2-minute isometric contractions. The exaggerated vagal response following contraction three is unexplained at this time, but may be important for beneficial
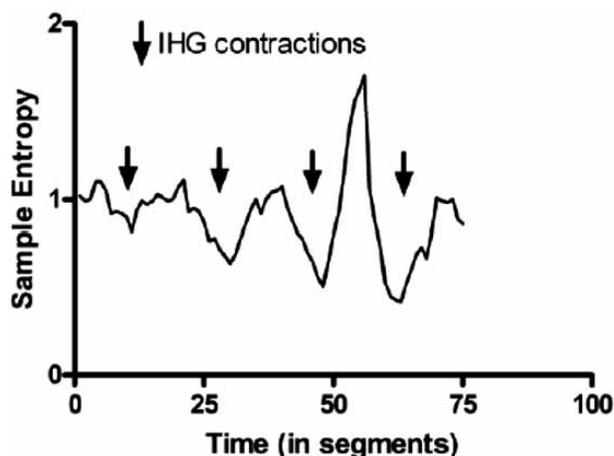
Fig. (2). Non-linear heart rate analysis (Sample Entropy) during acute isometric handgrip.

training adaptations. It also remains to be determined how long this effect is maintained, however, these results do demonstrate favorable ANS changes with acute IHG.

There are numerous potential mechanisms implicated in the reduction of resting ABP following IHG training. These include alterations in oxidative stress, improved endothelium-dependent vasodilation, and the modulation of the ANS. An alternative mechanism yet to be examined is the adaptation of baroreceptor sensitivity/functioning with IHG. Further research is required to conclusively elucidate the exact mechanisms responsible for the improvements in resting ABP following IHG training.

CLINICAL APPLICATIONS AND SIGNIFICANCE

Investment of Time

Time is a major determinant for exercise adherence [39] and participation in leisure time physical activity commonly decreases throughout ones lifespan [40]. The current position stand of the American College of Sports Medicine (ACSM) recommends >3hr/wk of aerobic exercise for hypertensive therapy [41]. However, unlike common exercise prescriptions (i.e. aerobic and/or resistance) and alternative lifestyle modifications, IHG training requires little adjustment in daily routine. The most commonly used protocol involves only 33 minutes of training per week [17, 18, 23]. In addition, IHG therapy seems to yield a similar reduction in resting ABP [23] in comparison to conventional aerobic therapy [42, 43]. The reduced time commitment may help to ease some of the barriers to exercise, and increase patient adherence. It should be noted that the position of the authors is not the recommendation of IHG training in place of, but rather as an adjunct to more conventional exercise therapies (i.e. aerobic or resistance training) and lifestyle modifications. Research has shown that patients participating in monitored exercise therapy can receive an additive benefit from IHG training [23].

Despite these promising results, there are few studies assessing the impact of various IHG training protocols. For instance, the results of protocols consisting of >4 contractions at various lengths, training intensities, and durations (i.e. >10-weeks) remains to be determined. The findings of an IHG longitudinal analysis reveal a linear reduction in resting ABP within 8-week training studies [21], therefore a study of longer duration may reveal the timeline for a plateau in resting ABP attenuations. Based on the available data, IHG may be considered a time-effective therapeutic option for HTN patients, but further investigations of optimal training protocols are required.

Associated Costs

The cost of anti-hypertensive medications remains a barrier for many HTN patients [3], as most HTN patients require more then one medication to adequately control ABP [1]. A retrospective analysis of HTN treatment within an internal medicine (Salt Lake City, UT, USA) clinic reported costs of $947, $575, and $420 for the first, second, and subsequent years, respectively. After the first year, they found anti-hypertensive medication costs to comprise 80% of the total treatment expense [44]. Likewise, common exercise modalities (aerobic/resistance training) typically require ongoing investments for equipment and/or memberships, often escalating associated costs. In contrast, IHG research has demonstrated hypotensive effects using simple spring handgrip trainers. The cost of these spring handgrip devices is often less than $5 USD. The present data suggests that IHG training may be used as a cost-effective therapy for HTN patients.

RECOMMENDATIONS FOR FUTURE RESEARCH

The most important recommendation to emerge from this review is the need for a major multi-centred, randomized control trial. This may help validate the results of smaller single-centred investigations. Similarly, independent research exploring variations in training prescription (frequency, duration, intensity) is required in order to maximize patient outcomes, since the current IHG protocol is perpetuated by continued success and not scientific research. This type of forward-thinking progressive research will help provide evidence for this time-efficient and cost-effective HTN therapy.

The examination of different handgrip training devices also needs to be considered. Though spring handgrip devices resulted in a significant training effect, the non-supervised prescription of these devices may be difficult in certain patient populations. A suitable handgrip device would allow patients to optimize training effects while providing sufficient instruction to prevent confusion and supervision. It is also necessary to explore the effectiveness of isometric training using different muscle groups. The initial evidence regarding the benefits of isometric exercise originates from longshoreman who completed both upper and lower body isometric exercise [15]. To our knowledge, Howden and colleagues (2002) have completed the only reported study on the effects of leg isometric training on resting ABP [45]. Leg isometric contractions were completed by contracting the knee extensors at a knee joint angle of 120 degrees. Participants trained 3d.wk^{-1} for 5-weeks at 20% of MVC, with four 2-min bilateral contractions per session. Training resulted in

a reduction of SBP (120.7 ± 9.6 to 110.7 ± 8.4 mmHg, p<0.05) while DBP remained unchanged (70.3 ± 7.4 to 66.7 ± 11.2 mmHg). Following leg isometric training participants had an 8-week washout before completing 5-weeks of IHG training. The difference in the magnitude of SBP reductions between these training modes (i.e. leg *vs.* arm) was not significant [45]. Isometric training with muscle groups other than the hand and forearm may provide alternatives for patients unable to complete handgrip exercise due to arthritis or other physical limitations. The adaptations to different training modes remain unclear.

One important facet for future research to explore is the use of IHG training in different patient populations. While it is advantageous for researchers to utilize similar samples for study comparison, the inclusion of alternative samples may assist in the validation of this therapy. For example, the use of IHG in preeclampsia patients may help to reduce resting ABP and associated maternal and infant morbidity and mortality. The transference of benefits outside of the HTN population currently remains unknown and unexamined. Lastly, IHG research must maintain its focus on clinical relevance to truly provide benefits to patients worldwide.

CONCLUSIONS

In summary, the available IHG data suggest that 8-weeks of training are sufficient to attenuate resting ABP, independent of medication. These effects are observed in both the normotensive and hypertensive populations. The underlying pathway responsible for these training effects likely involves the modulation of the autonomic nervous system. The clinical benefits of this novel therapy transcend cost and time, and may provide patients an alternative method of controlling their blood pressure.

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