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Isometric handgrip training lowers blood pressure and increases heart rate complexity in medicated hypertensive patients

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Hypertension is characterized by elevated blood pressure (BP) and autonomic dysfunction, both thought to be improved with exercise training. Isometric handgrip (IHG) training may represent a beneficial, time-effective exercise therapy. We investigated the effects of IHG training on BP and traditional and nonlinear measures of heart rate variability (HRV). Pre- and post-measurements of BP and HRV were determined in 23 medicated hypertensive participants (mean ± SEM, 66 ± 2 years) following either 8 weeks of IHG training ($n = 13$) or control ($n = 10$). IHG exercise consisted of four unilateral 2-min isometric contractions at 30% of maximal voluntary contraction, each separated by 4 min of rest. IHG training was performed 3 days/week for 8 weeks. IHG training decreased systolic BP (125 ± 3 mmHg to 120 ± 2 mmHg, $P < 0.05$) and mean BP (90 ± 2 mmHg to 87 ± 2 mmHg, $P < 0.05$), while sample entropy was increased (1.07 ± 0.1 to 1.35 ± 0.1, $P < 0.05$) and the fractal scaling distance score was decreased (0.34 ± 0.1 to 0.19 ± 0.1, $P < 0.05$). No significant changes were observed in traditional spectral or time-domain measures of HRV or control participants. IHG training improves nonlinear HRV, but not traditional HRV, while reducing systolic and mean BP. These results may highlight the benefits of IHG training for patients with primary hypertension.

Hypertension or the chronic elevation of arterial blood pressure (BP) is a major risk factor for cardiovascular disease morbidity and mortality (Chobanian et al., 2003). A hallmark feature of primary hypertension is dysfunction of the autonomic nervous system, primarily manifested as parasympathetic withdrawal and/or excessive sympathetic activation (Julius, 1991). The recommended frontline therapies in hypertension management are lifestyle modifications, such as healthy diet, smoking cessation, and exercise training (Chobanian et al., 2003). Aerobic exercise training has consistently been shown to reduce BP and improve autonomic function (Fagard & Cornelissen, 2007); however, the efficacy of additional forms of exercise training, such as resistance and isometric are less known (Pescatello et al., 2004). As detailed in recent meta-analyses (Kelley & Kelley, 2010; Owens et al., 2010) isometric handgrip (IHG) and leg training are intriguing exercise alternatives which require substantially less time (~30–75 total min/week) while documenting significant reductions in resting BP in normotensive and medicated hypertensive populations (Wiley et al., 1992; Ray & Carrasco, 2000; Howden et al., 2002; Taylor et al., 2003; McGowan et al., 2007; Millar et al., 2008; Wiles et al., 2010) similar to aerobic exercise training (Fagard & Cornelissen, 2007). Less consistent is the effects of isometric training on measures of autonomic function, with studies reporting improvements (Taylor et al., 2003) or no change (Ray & Carrasco, 2000; Wiles et al., 2010). Thus, at present, the effects of isometric training on the modulation of autonomic function remains debated.

Heart rate variability (HRV) is the most common method used to indirectly quantify cardiac autonomic modulation. HRV, conducted in either the time or spectral domain, measures the magnitude of heart rate (HR) fluctuations, which are related to the beat-to-beat regulation of HR by autonomic inputs (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In general, patients with hypertension demonstrate reduced spectral and/or time measures of HRV (Singh et al., 1998; Wu et al., 2008). However, the investigation of cardiac autonomic modulation using traditional spectral or time-domain measures of HRV may not be adequate to detect small changes in neurocardiac modulations. HR, like many physiological processes, is highly variable and nonstationary, even during steady-state conditions, and the result of both harmonic and fractal components (Yamamoto & Hughson, 1994). As a result, nonlinear measures of HRV have been proposed as important markers, sensitive to subtle but important modulations in HR behavior (Mäkikallio et al., 2002). In support, recent studies have demonstrated significant changes in nonlinear HRV measures, although traditional spectral or time-domain measures of HRV remain unaltered (Heffernan et al., 2007; Millar et al., 2009a, b). Physiologically, the genesis of nonlinear fluctuations in HR behavior are primarily the result of cardiac vagal activity (Yamamoto & Hughson, 1994; Hagerman et al., 1996; Tulppo et al., 2005; Millar et al., 2010), though sympathetic modulations may also be important (Hagerman et al., 1996; Tulppo et al., 2001a, 2005). As a result, nonlinear measures of HRV have been proposed to be markers of sympathovagal interactions, reflecting the balance of the cardiac autonomic state (Porta et al., 2007). Taken together, the use of nonlinear HRV measures may represent a novel tool to investigate the effects of IHG training on cardiac autonomic modulation.

Therefore, the purpose of this study was to examine the effects of IHG training on two measures of nonlinear HRV, sample entropy, and the short-term fractal scaling exponent in older participants medicated for hypertension. We hypothesized that IHG training would increase sample entropy, a marker of HR complexity, and improve fractal scaling properties, reflecting beneficial modulations in cardiac autonomic function, while also reducing BP.

Methods

This study consisted of 13 participants undertaking IHG training (65 ± 6 years of age, ♀ = 2) and 10 reference participants undertaking control conditions (67 ± 6 years of age, ♀ = 3). All participants were recruited from the local community (Hamilton, ON, Canada) and had to be between 55–80 years of age and medicated for hypertension. The average length of antihypertensive treatment(s) [mean (range)] in the training and controls groups was 9 (1–26) years and 7 (3–19) years, respectively. Participants were given a standardized health questionnaire and excluded if they had diabetes, congestive heart failure, took hormone supplements or regular nitrate medications, were current smokers, and/or possessed physical limitations preventing handgrip exercise. Additionally, six training participants and three control participants reported that they were previously diagnosed with coronary artery disease (> 1 year) in the health questionnaire. The participants were allocated based on a nonrandomized cohort design. The McMaster University Research Ethics Board approved this study protocol and all participants provided informed written consent prior to participation.

All participants completed a familiarization visit to the laboratory and testing environment, followed by a baseline measurement session to assess resting supine cardiovascular measures. In all cases, BP and HR were measured according to the protocols and procedures described below after 10 min of supine rest. Within 1 week of baseline testing, participants began IHG training (3×/week for 8 weeks) or the non-IHG control period. Following training or control, participants completed a post-measurement session within 7 days of completing the 8-week intervention period. All assessments of HR and BP were conducted in a quiet, temperature-controlled room following a participant-monitored 4-h fast, 12-h abstinence from caffeine, and a 24-h abstinence from vigorous exercise. All post-testing was conducted within 2 h of initial pretesting time of day, and the time of medication ingestion was standardized. Data collection was completed with the aid of Powerlab acquisition equipment (ADInstruments Inc., Colorado Springs, CO, USA) and Chart software (V5.4.2, ADInstruments Inc). Resting HR was collected in the supine position using single lead electrocardiography. Data were collected at a sampling rate of 1000 Hz to ensure an accurate R spike and visually inspected offline to exclude any aberrant beats, which accounted for < 1% in each participant. Pre- and post-IHG training resting HR analysis measures were conducted on ~500 R-R intervals. Resting BP was measured in the right brachial artery using a calibrated automated brachial oscillometric system (CBM-7000, Colin Medical Instruments, San Antonio, TX, USA) following 10 min of supine rest. Participants rested with their right arm supported at heart level. As recommended (Pickering et al., 2005), three BP measures were obtained following the 10-min rest period, each separated by at least 1 min and then averaged.

Training was performed unilaterally using their nondominant hand (left hand in all cases) with the aid of a programmed, digital hand dynamometer (CardioGrip Corp, IBX H-101, MD Systems, Westerville, OH, USA). As previously described (McGowan et al., 2006), the IHG protocol consisted of two maximum voluntary contractions (MVC) of the hand flexor muscles, followed by four 2-min contractions completed at 30% of MVC and separated by 4-min rest periods (i.e., 24 min/session). The handgrip device provided visual feedback to ensure compliance with the training intensity (i.e., maintaining a contraction of 30% MVC). Exercise trainers supervised two of the weekly training sessions at the laboratory, while participants carried out the third session independently at home. All training sessions were separated by a minimum of 1 day of rest. Participants were required to complete training log books recording the date of exercise, their MVC for each training session, and a summary compliance score provided by the handgrip device indicating the percentage of time during which the participant had maintained the 30% MVC threshold throughout each contraction. In all cases, compliance scores were ≥ 90%. In comparison, the control participants completed the pretesting session following by an 8-week nonintervention rest period, and the post-testing session.

All analysis of linear and nonlinear HRV was conducted with the aid of Kubios HRV Analysis Software 2.0 for windows (The Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland). This software is distributed free of charge upon request (http://venda.uku.fi/research/biosignal). In the time domain, the standard deviation of normal R-R intervals (SDNN), the root mean square of successive R-R interval differences (RMSSD) and the percentage of consecutive R-R intervals that differ by more than 50 ms (pNN50) are reported. In the frequency domain, the power spectra were quantified by measuring the area under two frequency bands: low-frequency (LF) power (0.04–0.15 Hz) and high-frequency (HF) power (0.15–0.4 Hz). The HF and LF spectral values are presented in both natural logarithm transforms (ln ms^2) and normalized units (nu).

The nonlinear measures assessed in this study were sample entropy and the short-term fractal scaling exponent (α_1). Sample entropy quantifies HR complexity and is defined as the negative natural logarithm of an estimate for the predictability in finding specific patterns or matches in a short-time series and has been previously described in detail (Richman & Moorman, 2000). In a highly predictive signal, sample entropy will have values approaching 0, while a highly unpredictable signal will have values close to 2 (Richman & Moorman, 2000). To characterize the stringency of pattern recognition, the length (m) of the subseries and the tolerance (r) of the matches are set by the user. Dimension m describes the length of the segments to be compared, while r sets the interval for tolerance to accept matches. In accordance with the analysis software, m was fixed at 2 while the filter parameter r was set at 20% of the standard deviation of the time series.

Detrended fluctuation analysis (DFA) was used to assess the fractal or self-similar correlations of the time series, and has been previously described in detail (Peng et al., 1995). In short, DFA is a modified root mean square analysis of a random walk, whereby the time series is integrated and divided into boxes of equal length.

Table 1. Participant baseline characteristics

Characteristic	Training	Control
n (♀)	13 (♀ = 2)	10 (♀ = 3)
Age (years)	65 ± 6	67 ± 6
Height (m)	1.76 ± 0.1	1.74 ± 0.1
Weight (kg)	85 ± 17	79 ± 12
Body mass index (kg/m^2)	27 ± 4	26 ± 3
Systolic blood pressure (mmHg)	125 ± 12	128 ± 16
Diastolic blood pressure (mmHg)	78 ± 2	75 ± 8
Established CAD (number)	6	3
Anti-hypertension medication use (years, range)	9 (1–26)	7 (3–19)
Medication classification (number)		
Ace inhibitor	5	4
ß-blocker	1	2
Calcium channel blocker	1	0
Diuretic	1	1
Ace inhibitor + ß-blocker	3	1
Ace inhibitor + calcium channel blocker	1	0
Ace inhibitor + diuretic	1	2

Values presented as mean ± SD.

ACE, angiotensin converting enzyme; CAD, coronary artery disease; mmHg, millimeters of mercury.

A least squares line is then fit to the data in each box, which is then detrended by subtracting the trends in each box (Peng et al., 1995; Goldberger et al., 2000). This calculation is repeated over all time scales (box sizes) to describe the relationship between the average fluctuation and the box size. The scaling exponent α corresponds to the slope of this line, which relates (log) fluctuation to (log) window size (Peng et al., 1995; Goldberger et al., 2000). The α exponent has also been described as a measure of "*roughness*" in the time series, with larger values representing a smoother time series and vice versa. A α_1 value near 1.0 is thought to reflect pink noise or a fractal-like signal (1/*f* noise) and is associated with healthy HR dynamics (Goldberger et al., 2000). A value of 1.0 or 1/*f* noise is thought to be beneficial, as it represents a balance between the bidirectional collapse of α_1 toward the complete unpredictability of white noise ($\alpha = 0.5$) or the predictability of Brownian noise ($\alpha = 1.5$) (Peng et al., 1995; Goldberger et al., 2000). The short-term (4 to 16 beats) scaling exponent (α_1) was used to analyze all R-R interval data in this study.

Two-way analysis of variance for repeated measures was used to examine potential differences in hemodynamic and HRV measures between groups (IHG and control) and time (pre- and post-), with Tukey post-hoc procedures used as necessary. In addition, normality of HRV measures was assessed using the Kolmogorov–Smirnov tests with data undergoing logarithmic transform as required. All statistical analyses were performed using SigmaStat for Windows 3.1 (Systat Software Inc., San Jose, CA, USA). Statistical significance was set at $P < 0.05$. All results are presented as mean ± SEM, unless otherwise noted.

Results

All participants ($n = 23$) completed the required IHG training or control sessions of this study. There was no change in participants' prescribed medications over the course of the study. Participant characteristics are detailed in Table 1. Importantly, participant characteristics, BP, HR, and HRV at baseline were not significantly different between the training and control groups ($P > 0.05$).

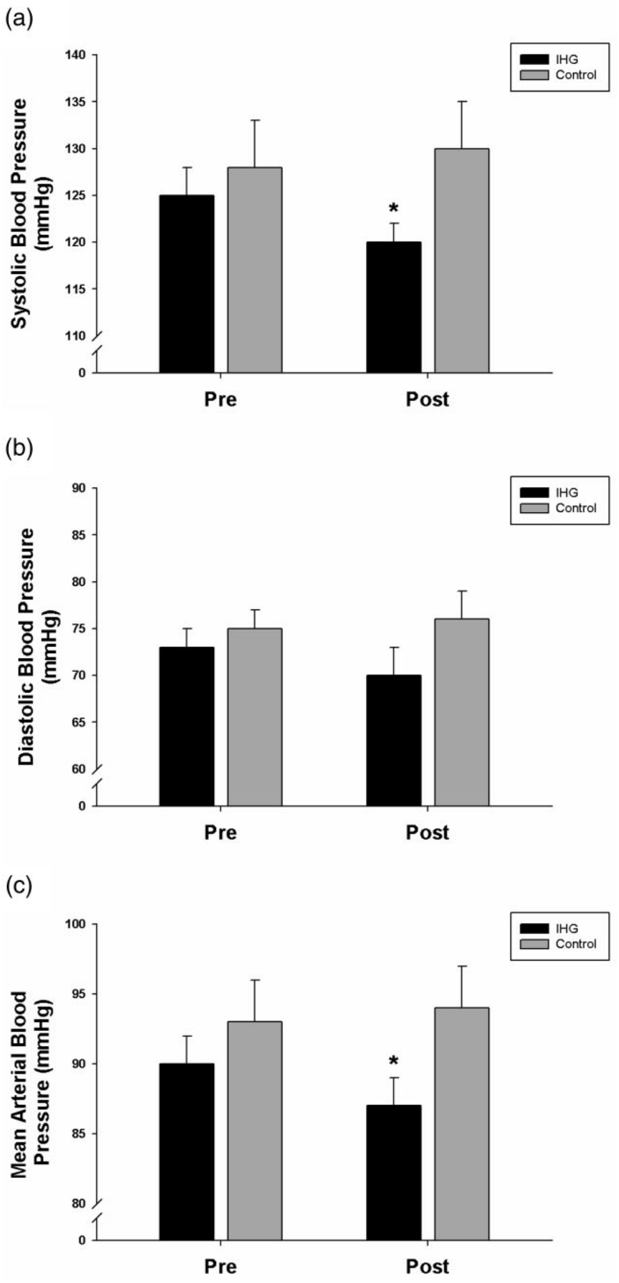

Fig. 1. Effects of 8 weeks of isometric handgrip (IHG) training on (a) systolic blood pressure (SBP), (b) diastolic blood pressure (DBP) and (c) mean arterial blood pressure (MAP). Values represent means ± SEM. *, significant difference from Pre ($P < 0.05$).

IHG training resulted in significant reductions in systolic BP (SBP) and mean arterial blood pressure (MAP) (Fig. 1). Specifically (mean ± SEM), SBP decreased in the training group (125 ± 3 mmHg to 120 ± 2 mmHg, $P < 0.05$) compared to control participants (128 ± 5 mmHg to 130 ± 5 mmHg, $P > 0.05$), while MAP also decreased in the training group (90 ± 2 mmHg to 87 ± 2 mmHg, $P < 0.05$) compared to control participants (93 ± 3 mmHg to 94 ± 3 mmHg, $P < 0.05$). In contrast, analysis of diastolic BP (DBP)

Table 2. Heart rate variability (HRV) measures pre- and post-8 weeks of isometric handgrip exercise training

	Pre	Post
IHG group		
Mean HR (1/min)	58 ± 2.8	56 ± 2.1
SDNN	49.9 ± 5.5	50.4 ± 6.8
RMSSD (ms)	30.2 ± 4.9	27.0 ± 2.7
pNN50 (%)	4.5 ± 0.9	5.4 ± 1.4
LF (ln ms^2)	6.1 ± 0.3	6.1 ± 0.3
HF (ln ms^2)	0.2 ± 0.3	5.5 ± 0.3
LF (nu)	65.6 ± 4.8	63.4 ± 3.8
HF (nu)	34.3 ± 4.9	36.6 ± 3.8
LF/HF ratio	2.65 ± 0.5	2.16 ± 0.4
Sample entropy	1.07 ± 0.1	1.35 ± 0.1*
$\lvert 1 - \alpha_1 \rvert$	0.34 ± 0.1	0.19 ± 0.1*
Control group		
Mean HR (bpm)	62 ± 2.7	63 ± 2.9
SDNN	42.6 ± 6.5	38.1 ± 3.9
RMSSD	24.5 ± 3.9	24.8 ± 3.9
pNN50 (%)	4.1 ± 1.3	4.7 ± 1.7
LF (ln ms^2)	5.6 ± 0.4	5.4 ± 0.2
HF (ln ms^2)	5.0 ± 0.3	4.9 ± 0.3
LF (nu)	60.1 ± 5.4	60.9 ± 4.9
HF (nu)	39.9 ± 5.4	39.1 ± 4.9
LF/HF ratio	2.22 ± 0.5	2.27 ± 0.5
Sample entropy	1.25 ± 0.4	1.23 ± 0.2
$\lvert 1 - \alpha_1 \rvert$	0.32 ± 0.1	0.31 ± 0.1

*Significant difference compared to Pre, $P < 0.05$. Values presented as mean ± SEM.

bpm, beats per minute; HR, heart rate; HF, high frequency; ln, natural logarithm; LF, low frequency; ms, milliseconds; min, minute; nu, normalized units; pNN50, percentage of consecutive RR intervals that differ by more than 50 ms; RMSSD, root mean square of successive RR interval differences; SDNN, standard deviations of normal R-R intervals; α_1, short-term fractal scaling exponent.

revealed a trend for an interaction effect ($P = 0.10$) between training participants (73 ± 2 mmHg to 70 ± 3 mmHg) and control participants (75 ± 2 mmHg to 76 ± 3 mmHg).

The effects of IHG training and control conditions on HRV can be seen in Table 2. In short, each of the frequency and time-domain measures, including HR, were not significantly different over time or between groups ($P > 0.05$). In contrast, there was a significant interaction effect for sample entropy as values increased following IHG training ($P < 0.05$) but were unchanged in the control group ($P > 0.05$). Analysis of the short-term fractal scaling exponent demonstrated no significant effects ($P > 0.05$). However, analysis of the fractal distance score, used to correct for potential bidirectional response patterns of α_1 (Millar et al., 2009b; Mendonca et al., 2010), did reveal a significant interaction effect as $\lvert 1 - \alpha_1 \rvert$ values were reduced following IHG training ($P < 0.05$) but not control ($P > 0.05$).

Discussion

The main finding of this study is that 8 weeks of IHG training results in significant reductions in SBP and MAP and modulations in nonlinear measures of HRV. Specifically, IHG training was associated with increases in sample entropy and decreases in the fractal scaling distance score, both considered to be markers of improved sympathovagal interactions. In contrast, traditional spectral and time-domain measures of HRV were unchanged with IHG training. The results of this study suggest that IHG training may be considered a beneficial therapy for medicated hypertensive patients, as a means to reduce BP and improve cardiac autonomic function.

Effects of IHG training on resting BP

The hemodynamic results of this study confirm previous findings in medicated hypertensive participants (Taylor et al., 2003; McGowan et al., 2007), which reported significant reductions in SBP and/or DBP following IHG training. One novel feature of the current study is the low pre-training baseline BP in the training group. This is important as it demonstrates that even in well-controlled medicated hypertensive participants, IHG training has significant BP effects. The practical application of this finding is the potential reduction in current antihypertensive pharmacological therapies. Although our sample was of well-controlled hypertensive participants, the results may be extrapolated to more at risk populations as pre-training systolic BP is correlated with IHG training results (Millar et al., 2007). Thus, while the clinical impact of IHG training appears high, the underlying physiology warrants further investigation. The difficulty in establishing the pathways involved in IHG training-associated reductions in BP has been recently underscored by Wiles et al. (2010), who reported reductions in SBP and MAP with leg isometric training, even though cardiac output and total peripheral resistance remained statistically unaltered. This may suggest that the mechanisms responsible for IHG training adaptations are multifactorial and the result of small changes in multiple regulatory pathways.

Effects of IHG training on traditional measures of HRV

Presently, only two investigations have studied the effects of isometric training on spectral HRV. Taylor et al. (2003) reported increases in HF area, related to increased vagal modulation (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), in addition to large (> 10 mmHg) mean reductions in seated SBP and MAP following 10 weeks of IHG training in older medicated hypertensive participants. In contrast, Wiles et al. (2010) demonstrated no significant modulations in spectral HRV following 8 weeks of isometric leg training in young normotensive participants, though modest (< 6 mmHg) mean reductions in SBP, DBP, and MAP were reported. The results of the current study confirm the findings of Wiles et al. (2010), as spectral and time-domain measures of HRV were unchanged (Table 2), although modest reductions (< 6 mmHg) in SBP and MAP were detected. Taken together, these results may suggest that either modest IHG training adaptations do not alter traditional measures of HRV or that measures of traditional HRV are insensitive to small changes in neurocardiac modulation present with modest reductions in BP.

Effects of IHG training on nonlinear measures of HRV

A novel finding of this study is the increase in HR complexity (i.e., sample entropy) and decrease in the fractal scaling distance score. These results are similar to those reported by our laboratory following an acute bout of IHG exercise (Millar et al., 2009a), and those reported following aerobic and resistance training (Tulppo et al., 2003; Heffernan et al., 2007). The increase in sample entropy suggests that the HR signal has become more complex and less predictable, while the decrease in the fractal scaling distance score suggests that the HR signal has moved closer toward 1 or 1/*f* noise, an improved balance between complete randomness and predictability of the HR signal (Goldberger et al., 2000). Previous research suggests that sample entropy and α_1 may both represent general markers of dynamic sympathovagal interactions (Porta et al., 2007), although mounting evidence suggests that shifts in nonlinear HRV with pharmacological (Hagerman et al., 1996; Penttilä et al., 2003; Lepoluoto et al., 2005; Tulppo et al., 2001b, 2005; Millar et al., 2010), postural (Tulppo et al., 2001a; Porta et al., 2007), and/or interventions (i.e., exercise, water immersion; Tulppo et al., 2001a, 2003; Millar et al., 2010) are strongly reflective of underlying changes in cardiac vagal modulations. Thus, the observed changes in nonlinear HRV measures may support the findings of Taylor et al. (2003), reflective of improved cardiac vagal modulation following IHG training. The clinical significance of these changes in nonlinear measures of HRV remains to be substantiated, although reduced HR complexity (i.e., sample entropy) has been demonstrated to precede paroxysmal atrial fibrillation (Vikman et al., 1999) and correlate with postoperative surgical complications (Fleisher et al., 1993), while reduced short-term fractal scaling properties are associated with ventricular arrhythmias (Mäkikallio et al., 1997, 1999) and mortality (Huikuri et al., 2000). Thus, IHG training may produce additional benefits other than reductions in BP, related to improvements in cardiac autonomic function.

Study limitations

As mentioned, the heterogeneous sample population possessed well-controlled BP and future studies should seek to confirm these findings in newly diagnosed unmedicated or resistant hypertensive patients to the enhance clinical benefit. The medication status of the sample population is also diverse, with the effects of long-term antihypertensive therapy on adaptations of cardiac autonomic modulation and HRV following exercise training largely unknown. The sample size utilized in this study was not sufficient to address potential relationships between antihypertensive class and specific IHG training adaptations. Additionally, a large, but non-significant difference in baseline sample entropy existed between intervention and control participants; future studies may require participant stratification based on baseline autonomic status. With these limitations in mind, this investigation is the first to describe changes in nonlinear HRV following IHG training, while further providing evidence for hypotensive training effects.

In conclusion, 8 weeks of IHG training reduce SBP and MAP concomitant with increases in HR complexity (i.e., sample entropy) and reductions in the fractal scaling distance score, thought to be indicative of improvements in cardiac autonomic modulation, in older participants medicated for hypertension. This work adds to a growing body of literature demonstrating beneficial effects of isometric exercise training. IHG training may represent a beneficial therapy for patients with elevated BP and autonomic dysfunction.

Perspectives

The estimated percentage of treated hypertensive patients with BP values still above target (i.e., 140/90 mmHg) is a staggering 42% (Ong et al., 2007). The ability of IHG training to reduce BP yields interesting clinical applications. Aerobic exercise has traditionally been recommended as a primary or adjunct therapy to reduce BP (Chobanian et al., 2003), although the long-term adherence to aerobic exercise training is hindered by patients described "lack of time" to fulfill the recommended activity prescription of moderate intensity exercise for 30 + min on 5 days per week (Haskell et al., 2007). The ability of IHG training to lower BP in half of the required time, may improve exercise adherence. Key to the adoption of IHG as a beneficial form of exercise is the elucidation of the mechanisms responsible for its mode of action. The dysfunction of the autonomic nervous system is an integral component of hypertension (Julius, 1991) and may be a mechanism for observed reductions in BP. Further evaluation of potential pathways involved in IHG training adaptations in BP and autonomic function are necessary.

Key words: heart rate, dynamics, blood pressure, isometric exercise, autonomic nervous system.

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